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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 491/052, 495/04, 311/22
C07D 335/06, 405/04, 409/04
// (C07D 491/052, 311/00, 231/00)
(C07D 495/04, 335/00, 231/00)

A1

(11) International Publication Number: WO 91/11448

(43) International Publication Date: 8 August 1991 (08.08.91)

(21) International Application Number: PCT/EP91/00154

(22) International Filing Date: 26 January 1991 (26.01.91)

(30) Priority data:

9002314.4	2 February 1990 (02.02.90)	GB
9002315.1	2 February 1990 (02.02.90)	GB
9002425.8	6 February 1990 (06.02.90)	GB

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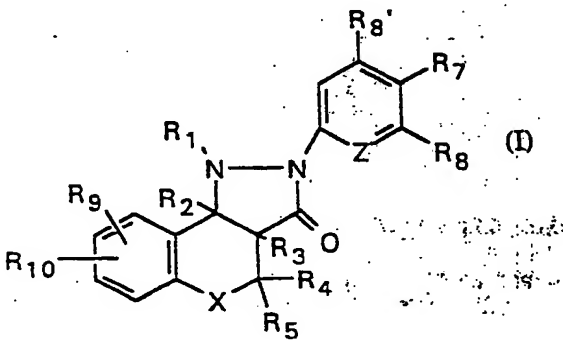
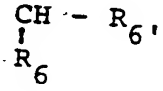
(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent).

Published
With international search report.

(54) Title: THERAPEUTIC AGENTS



(I)



(II)

(57) Abstract

Compounds of formula (I) in which X represents oxygen or sulphur; Z represents -CH= or -N= when X represents oxygen; Z represents -CH= when X represents sulphur; R_5 represents hydrogen when R_3 represents methyl, or R_5 represents (a), when R_3 represents a bond together with either one of R_2 and R_4; R_6 represents hydrogen, halo, $S(O)_nY_1$, carboxy, carbamoyl, a carboxylic acyl group, an esterified carboxyl group or $CONR_{12}R_{13}$; $R_{6'}$ represents hydrogen or methyl; or R_6 and $R_{6'}$ together with the carbon atom to which they are attached represent cyclopropyl; R_9 and R^{10}, which may be the same or different, represent halo; or R_9 represents hydrogen and R_{10} represents hydrogen, halo, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or a carboxylic acyloxy group; R_{12} represents methyl, ethyl or C_{3-8} cycloalkyl and R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocyclic group, a 5 or 6 membered heterocyclic aryl group or C_{3-8} cycloalkyl; or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or R_{12} and R_{13} together with the nitrogen to which they are attached represent a 3-8 membered non-aromatic heterocyclic group which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group; Y_1 represents C_{1-6} alkyl; n is 0, 1 or 2, and R_1, R_2, R_4, R_7, R_8 and $R_{8'}$ are as-defined, for use as immunomodulatory agents.

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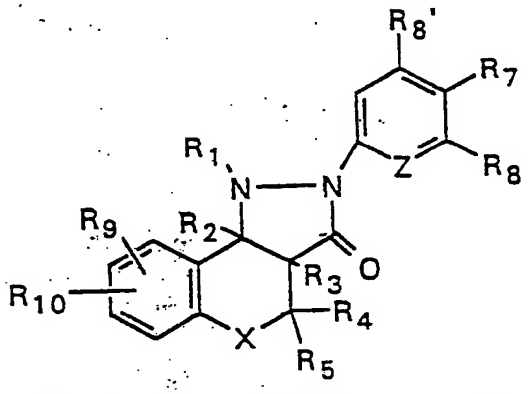
Therapeutic Agents

The present invention relates to novel therapeutic agents, and in particular to [1]benzopyrano[4,3-c]-pyrazoles or [1]benzothiopyrano[4,3-c]pyrazoles, to processes for their preparation, to pharmaceutical compositions containing them and to their therapeutic activity as immunomodulatory agents.

The present invention relates to compounds of formula I



I

in which X represents oxygen or sulphur;

when X represents oxygen or sulphur R_1 represents hydrogen or together with R_2 represents a bond; R_2 together with either one of R_1 and R_3 represents a bond; R_3 together with either one of R_2 and R_4 represents a bond; R_4 represents hydrogen or together with R_3 represents a bond;

or when X represents sulphur, R_1 and R_2 represent a bond, R_3 represents methyl and R_4 and R_5 represent hydrogen;

Z represents -CH= or -N= when X represents oxygen;

Z represents -CH= when X represents sulphur;

R_5 represents hydrogen when R_3 represents methyl,

or R_5 represents $\overset{R_6}{\underset{|}{CH}} - R_{6'}$,

when R_3 represents a bond together with either one of R_2 and R_4;

R_6 represents hydrogen, halo, $S(O)_nY_1$, carboxy, carbamoyl, a carboxylic acyl group, an esterified carboxyl group or $CONR_{12}R_{13}$;

$R_{6'}$ represents hydrogen or methyl;

or R_6 and $R_{6'}$ together with the carbon atom to which they are attached represent cyclopropyl;

R_7 represents hydrogen, halo, trifluoromethyl, C_{1-6} alkyl, methoxy or $S(O)_mY_1$;

R_8 represents hydrogen, halo or trifluoromethyl;

$R_{8'}$ represents hydrogen, halo or trifluoromethyl;

R_9 and R_{10}, which may be the same or different, represent halo; or R_9 represents hydrogen and R_{10} represents hydrogen, halo, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or a carboxylic acyloxy group;

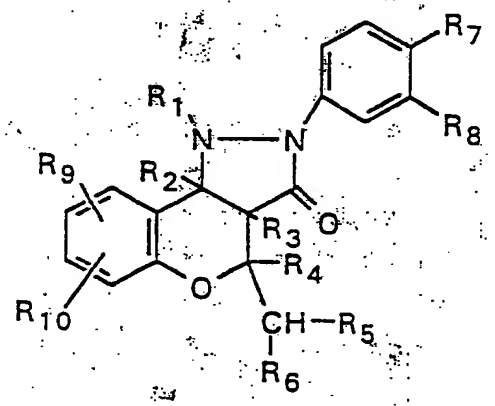
R_{12} represents methyl, ethyl or C_{3-8} cycloalkyl and R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocylic group, a 5 or 6 membered heterocyclic aryl group or C_{3-8} cycloalkyl; or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or

R_{12} and R_{13} together with the nitrogen to which they are attached represent a 3-8 membered non-aromatic heterocylic group which may be substituted by C_{2-6} acyloxy(C_{1-6})alkyl;

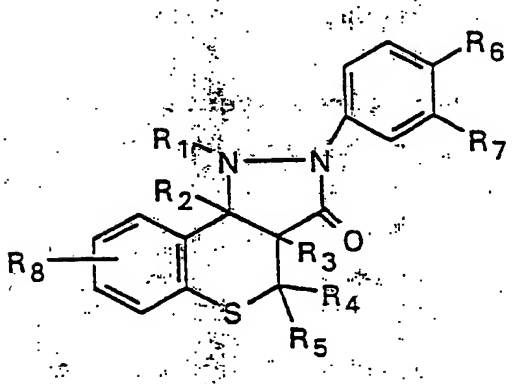
Y_1 represents C_{1-6} alkyl;
n is 0, 1 or 2 and m is 0 or 1

which have immunmodulatory activity.

In our copending patent applications (PCT patent application nos. PCT/GB 89/00859 and PCT/GB 89/00860) there are described certain compounds of formula A and formula B



A



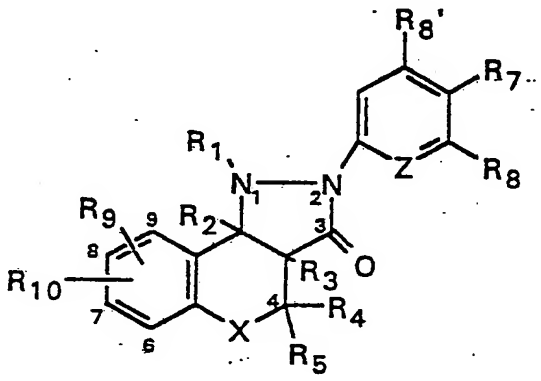
B

The first PCT patent application described above also discloses 4-methoxybenzyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate

as an intermediate compound without any therapeutic activity.

These compounds are excluded from the scope of the present invention.

Accordingly, the present invention provides novel compounds of formula I



I

in which X represents oxygen or sulphur;

when X represents oxygen or sulphur R_1 represents hydrogen or together with R_2 represents a bond; R_2 together with either one of R_1 and R_3 represents a bond; R_3 together with either one of R_2 and R_4 represents a bond; R_4 represents hydrogen or together with R_3 represents a bond;

or when X represents sulphur, R_1 and R_2 represent a bond, R_3 represents methyl and R_4 and R_5 represent hydrogen;

Z represents -CH= or -N= when X represents oxygen;

Z represents -CH= when X represents sulphur;

R_5 represents hydrogen when R_3 represents methyl,

or R_5 represents $\underset{R_6}{\overset{|}{CH}} - R_{6'}$,

when R_3 represents a bond together with either one of R_2 and R_4;

R_6 represents hydrogen, halo, $S(O)_nY_1$, carboxy, carbamoyl, a carboxylic acyl group, an esterified carboxyl group or $CONR_{12}R_{13}$;

$R_{6'}$ represents hydrogen or methyl;

or R_6 and $R_{6'}$ together with the carbon atom to which they are attached represent cyclopropyl;

R_7 represents hydrogen, halo, trifluoromethyl, C_{1-6} alkyl, methoxy or $S(O)_mY_1$;

R_8 represents hydrogen, halo or trifluoromethyl;

$R_{8'}$ represents hydrogen, halo or trifluoromethyl;

R_9 and R_{10}, which may be the same or different, represent halo; or R_9 represents hydrogen and R_{10} represents hydrogen, halo, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or a carboxylic acyloxy group;

R_{12} represents methyl, ethyl or C_{3-8} cycloalkyl and R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocylic group, a 5 or 6 membered heterocyclic aryl group or C_{3-8} cycloalkyl; or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or

R_{12} and R_{13} together with the nitrogen to which they are attached represent a 3-8 membered

non-aromatic heterocylic group which may be substituted by C_{2-6} acyloxy(C_{1-6})alkyl;

Y_1 represents C_{1-6} alkyl;
n is 0, 1 or 2 and m is 0 or 1

provided that:

I) when X is oxygen; Z = -CH= and:

a) R_6 represents C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy; or

b) when R_6 represents hydrogen, halo, $S(O)_nY_1$, carbamoyl, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkanoyl or when R_6 and $R_{6'}$ together with the carbon atom to which they are attached form cylopropyl then R_{10} represents a carboxylic acyloxy group other than C_{2-6} alkanoyloxy; or

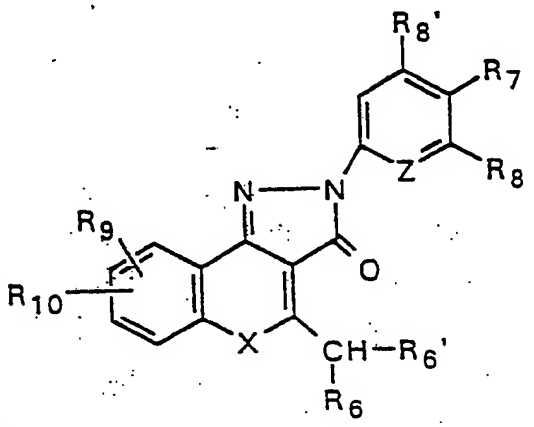
c) when R_1 and R_2 form a bond, R_3 and R_4 form a bond, $R_{6''}$, R_8, $R_{8'}$, R_9 and R_{10} each represent hydrogen, R_7 represents chloro, then R_6 does not represent 4-methoxybenzyloxycarbonyl;

II) When X is sulphur and a) R_3 represents methyl; or b) R_6 represents hydrogen, carboxy, $S(O)_nY_1$, C_{2-6} alkoxycarbonyl, carbamoyl or C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy.

It will be understood that a group containing a chain of 3 or more carbon atoms may be straight or branched, for example propyl includes n-propyl and isopropyl, and butyl includes n-butyl, sec-butyl,

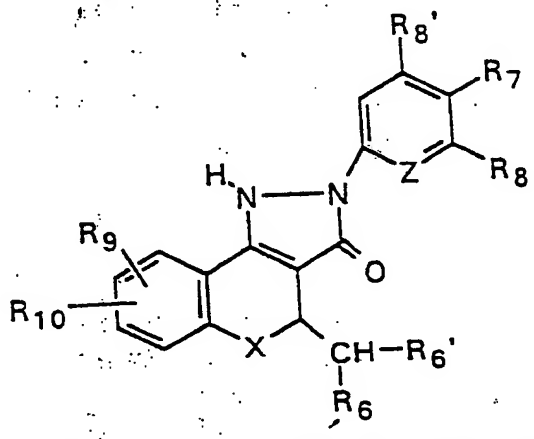
isobutyl and tert-butyl. The term "halo" includes fluoro, chloro or bromo.

In one class of compounds of formula I, R_1 and R_2 form a bond and R_3 and R_4 form a bond, as represented by formula II



II

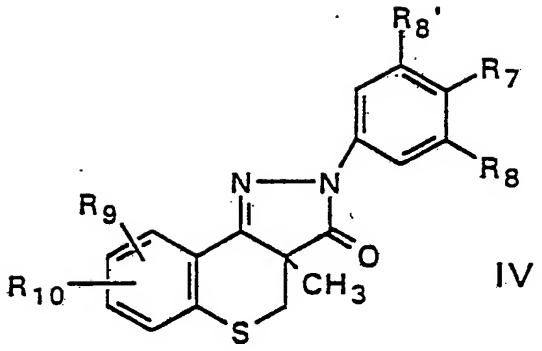
and R_6, R_6', R_7, R_8, R_8', R_9 and R_{10} are as hereinabove defined. In another class of compounds of formula I, R_1 represents hydrogen, R_2 and R_3 form a bond and R_4 represents hydrogen, as represented by formula III



III

and R_6, R_6', R_7, R_8, R_8', R_9 and R_{10} are as hereinabove defined.

In another class of compounds of formula I, R_1 and R_2 form a bond, and R_4 and R_5 represent hydrogen, as represented by formula IV



IV

and R_7, R_8, $R_{8'}$, R_9 and R_{10} are as herein defined. Preferred substituents are as given hereinafter. More preferably R_7 represents halo or trifluoromethyl, R_8 represents hydrogen or halo, R_8' represents hydrogen or halo and R_9 represents hydrogen.

In compounds of formula I, preferably R_6' represents hydrogen.

In certain compounds of formula I, the group R_6 may be an esterified carboxyl group, a carboxylic acyl group or certain tertiary carboxamide groups. These groups may be represented by the formula

$$-CO.R_{14}$$

in which R_{14} represents an alkoxy group (for example C_{1-6}); an alkenyloxy group (for example C_{2-6}); a cycloalkoxy group (for example C_{3-10}); an oxygen atom attached to a non-aromatic heterocyclic group; a carbocyclic aryloxy group; a heterocyclic aryloxy group; an alkyl group (for example C_{1-6}); an alkenyl group (for example C_{2-6}); a cycloalkyl group (for C_{3-10}); a non-aromatic heterocyclic group; a carbocylic aryl group; or a heterocyclic aryl group each of the groups being optionally substituted. Readily hydrolysable esters and amides as defined herein are included within the scope of the present invention as

well as those which are less readily hydrolysable. Also included are certain tertiary carboxamido groups. Some compounds of formula I may contain a substituted acetyl group in the 4-position of the ring system. In certain preferred compounds of formula I the group R_6 may have the formula

a) $-CO.OR_{15}$

b) $-CO.R_{16}$

c) $-CO.NR_{12}R_{13}$

in which R_{12} represents methyl, ethyl or C_{3-8} cycloalkyl and R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocyclic group, a 5 or 6 membered heterocyclic aryl group or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or R_{12} and R_{13} together with the nitrogen to which they are attached represent a 3-8 membered non-aromatic heterocyclic group which may be substituted by C_{2-6} acyloxy(C_{1-6})alkyl; R_{15} and R_{16} represent C_{1-6} alkyl; C_{2-6} alkenyl; C_{3-10} cycloalkyl; a 3-8 membered non-aromatic heterocyclic group, a phenyl group or a 5 or 6 membered heterocyclic aryl group; each of the groups R_{15}, R_{16} being optionally substituted by Z.

Z represents Z_1, Z_2, phenyl, a 3-8 membered non-aromatic heterocyclic group (preferably containing one or two heteroatoms selected from oxygen, sulphur or nitrogen), a 5-6 membered heterocyclic aryl group (preferably containing one to three heteroatoms selected from oxygen, sulphur or nitrogen), each group being optionally substituuted by Z_1 or Z_2;

Z_1 represents halo, trifluoromethyl, hydroxy, carboxy or cyano;

Z_2 represents C_{1-6} alkyl, C_{3-10} cycloalkyl, $S(O)mY_1$, $CONR_{18}R_{19}$, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, phenoxy, $NY_2Y_{2'}$, $NHCOY_2$ or $NHSO_2Y_2$ and each may be further substituted by Z.

Y_2 and $Y_{2'}$, which may be the same or different, each represent hydrogen, C_{1-6} alkyl or phenyl;

R_{18} and R_{19}, which may be the same or different, each represent hydrogen; C_{1-6} alkyl; C_{3-10} cycloalkyl, C_{2-6} alkenyl; a carbocyclic aryl group; a 3-8 membered non-aromatic heterocyclic group; a 5 or 6 membered heterocyclic aryl group; or R_{18} and R_{19} together with the nitrogen to which they are attached form a 3-8 membered non-aromatic heterocyclic group.

In compounds of formula I, suitable substituents R_6 include the following:
hydrogen; halo (fluoro, chloro or bromo), preferably fluoro or chloro, most preferably chloro; carboxy; carbamoyl, $S(O)nY_1$ in which Y_1 is preferably C_{1-4} alkyl and n represents 0, 1 or 2 (for example methylthio, ethylthio, propylthio, methylsulphinyl, ethylsulphinyl, propylsulphonyl), more preferably Y_1 is C_{1-2} alkyl, most preferably methyl; suitably n is 0 or 1 and preferably 0. Most preferably R_6 represents hydrogen or C_{2-6} alkoxycarbonyl.

In compounds of formula I', R_6 together with $R_{6'}$ and the carbon to which they are attached may form cyclopropyl.

Preferably R_6 also includes $CONR_{12}R_{13}$ in which R_{12} represents methyl or ethyl and R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocyclic group containing one

or two heteroatoms selected from oxygen, sulphur or nitrogen, a 5 or 6 membered heterocyclic aryl group containing one to three heteroatoms selected from oxygen, sulphur or nitrogen; or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl (for example methoxycarbonyl) or halo (for example chloro); or R_{12} and R_{13} together with the nitrogen to which they are attached form a 3-8 membered non-aromatic heterocyclic group which may contain a further heteroatom selected from oxygen, sulphur or nitrogen which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group (for example propionyloxyethyl).

Preferably R_6 also includes a carboxylic ester group, which is preferably represented by the formula

$$-CO.OR_{15}$$

in which R_{15} represents C_{1-6} alkyl; C_{2-6} alkenyl; C_{3-10} cycloalkyl; a 3-8 membered non-aromatic heterocyclic group containing one or two heteroatoms selected from oxygen, sulphur or nitrogen, a carbocyclic aryl group; a 5 or 6 membered heterocyclic aryl group containing one to three heteroatoms selected from oxygen, sulphur or nitrogen, each group being optionally substituted by Z. Preferably R_{15} represents C_{1-6} alkyl, C_{3-8} cycloalkyl, a 5-7 membered non-aromatic heterocyclic group containing one or two heteroatoms selected from oxygen, sulphur or nitrogen; a phenyl group; a 5 or 6 membered heterocyclic aryl ring containing one or two heteroatoms selected from oxygen, sulphur or nitrogen, each group being optionally substituted by Z.

Preferably R_6 also represents a carboxylic acyl group which is preferably represented by the formula

$$-CO.R_{16}$$

in which R_{16} represents C_{1-6} alkyl; C_{2-6} alkenyl; C_{3-10} cycloalkyl; a 3-8 membered non-aromatic heterocyclic group containing one or two heteroatoms selected from oxygen, sulphur or nitrogen; a carbocyclic aryl group; a 5 or 6 membered heterocyclic aryl group containing one to three heteroatoms selected from oxygen, sulphur or nitrogen; each group being optionally substituted by Z. Preferably R_{16} represents C_{1-6} alkyl, C_{3-8} cycloalkyl, a 5-7 membered non-aromatic heterocyclic group containing one or two heteroatoms selected from oxygen, sulphur or nitrogen; a phenyl group; a 5 or 6 membered heterocyclic aryl ring containing one or two heteroatoms selected from oxygen, sulphur or nitrogen, each group being optionally substituted by Z.

Preferably Z represents Z_1 or Z_2.

Preferably Z_1 represents halo (fluoro, chloro or bromo), more preferably fluoro or chloro, most preferably chloro; hydroxy or cyano;

Preferably Z_2 represents the following:

C_{1-6} alkyl, preferably C_{1-4} alkyl (for example methyl, ethyl or propyl), more preferably methyl or ethyl and most preferably methyl; C_{3-7} cycloalkyl, preferably C_{3-5} cycloalkyl; C_{1-6} alkoxy, preferably C_{1-4} alkoxy (for example methoxy, ethoxy or propoxy), more preferably methoxy or ethoxy, and most preferably methoxy; $S(O)_mY_1$ in which Y_1 is preferably C_{1-4} alkyl and m represents 0, 1 or 2, (for example methylthio, ethylthio, propylthio, methylsulphinyl, ethylsulphinyl, propylsulphinyl, methylsulphonyl, ethylsulphonyl, propylsulphonyl), more preferably Y_1 is C_{1-2} alkyl, most preferably methyl, suitably m is 0 or 1 and preferably 0; C_{2-5} alkoxycarbonyl (for example

methoxycarbonyl or ethoxycarbonyl); C_{2-5} alkanoyl (for example acetyl or propionyl); or C_{2-5} alkanoyloxy (for example acetoxy or propionyloxy); $CONR_{18}R_{19}$ in which R_{18} and R_{19} preferably represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, a 3-8 membered non-aromatic heterocyclic group containing one or two heteroatoms selected from oxygen, sulphur or nitrogen; phenyl, a 5 or 6 membered heterocyclic aryl group containing one to three heteroatoms selected from oxygen, sulphur or nitrogen; or R_{18} and R_{19} together with the nitrogen to which they are attached form a 3-8 membered non-aromatic heterocyclic group which may contain a further heteroatom selected from oxygen, sulphur or nitrogen, each of the substituents R_{18}, R_{19} being optionally substituted by Z.

In compounds of formula I, particularly preferred substituents R_6 include:

hydrogen, carboxy or $-CO.R_{14}$ in which R_{14} is as defined above.

Preferred esterified carboxyl groups R_6 include:

C_{2-6} alkoxycarbonyl (for example methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl or pentyloxycarbonyl; C_{3-8} cycloalkoxycarbonyl (for example cyclobutoxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) or tetrahydro-2H-pyran-4-yloxy-carbonyl, each of which groups may be substituted by: C_{1-6} alkyl (for example methyl); C_{3-8} cycloalkyl (for example cyclohexyl, cyclopentyl, cyclobutyl or cyclopropyl); phenyl; a 3-8 membered non-aromatic heterocyclic group containing one or two heteroatoms selected from nitrogen, oxygen or sulphur, (for example tetrahydrofuryl, tetrahydropyranyl, morpholino, piperidino, thiomorpholino, piperazino); a 5 or 6

membered aromatic heterocyclic group containing one to three atoms selected from oxygen, sulphur or nitrogen (for example pyridyl, thiazolyl, thienyl); C_{2-6} alkoxycarbonyl (for example ethoxycarbonyl); C_{2-6} alkanoyl (for example acetyl); C_{1-6} alkoxy (for example methoxy or ethoxy); $S(O)_mY_1$ (for example methylthio); C_{2-6} alkanoyloxy (for example acetoxy); cyano, hydroxy, acetamido, trifluoromethyl, halo. The optional C_{1-6} alkoxy substituent may further be substituted with C_{1-6} alkoxy (for example methoxy) or C_{2-6} alkanoyloxy (for example acetoxy). The optional phenyl, non-aromatic heterocyclic group or aromatic heterocyclic group substituent may further be substituted by C_{1-6} alkyl (for example methyl), C_{1-6} alkoxy (for example methoxy), halo (for example chloro).

In especially preferred compounds R_6 represents $CO_2(CH_2)_pJ$ in which p is 0-3 and J represents cyano, hydroxy, C_{3-8} cycloalkyl, C_{2-6} alkanoyloxy, C_{2-6} alkoxycarbonyl, C_{1-6} alkoxy, C_{1-6} alkoxy(C_{1-6})alkoxy, C_{1-6} alkylthio, or J represents a 5 or 6 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen; a 5 or 6 membered aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen; or a phenyl group, each of which groups is optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halo. Preferably p is 1 or 2.

Particularly preferred substituents R_6 also include a carboxylic acyl group which may be C_{3-8} cycloalkylcarbonyl (for example cyclopropylcarbonyl, cyclohexylcarbonyl); or C_{2-6} alkanoyl (for example acetyl, propionyl, butyryl, pentanoyl, hexanoyl), which may be substituted with phenyl or phenoxy each optionally substituted by halo, C_{1-4} alkyl, or C_{1-4} alkoxy; or C_{2-6} alkanoyl may be substituted with C_{2-6}

alkoxycarbonyl (for example methoxycarbonyl), C_{2-6} alkoxy (for example methoxy), C_{1-4} alkylthio (for example methylthio), C_{3-8} cycloalkyl (for example cyclopentyl).

In especially preferred compounds R_6 represents $COCH_2k$ in which k represents C_{1-4} alkoxy or phenoxy.

Particularly preferred substituents R_6 may also include the group $CONR_{12}R_{13}$ in which R_{12} represents methyl or ethyl, preferably methyl, and R_{13} includes phenyl or C_{1-4} alkyl (more preferably methyl or ethyl, and most preferably methyl) substituted with phenyl. Most preferably R_{12} represents ethyl and R_{13} represents phenyl.

Especially preferred substituents R_6 include hydrogen;
cyclopropylmethoxycarbonyl;
2-methoxybenzyloxycarbonyl; 4-chlorobenzyloxycarbonyl;
2-methylbenzyloxycarbonyl; 3-methylbenzyloxycarbonyl;
2-acetamidoethoxycarbonyl;
2-(2-methylpiperidino)ethoxycarbonyl;
3-(2-propionyloxyethyl)-3-azapentamethylenecarbamoyl;
methyl(2-methylphenyl)carbamoyl;
methyl(3-methylphenyl)carbamoyl;
methyl(4-methylphenyl)carbamoyl;
methyl(1,3-dioxolan-2-yl-methyl)carbamoyl;
chloro; bromo; methylthio; ethylthio; methylsulphinyl;
methylsulphonyl; carboxy; methoxycarbonyl;
ethoxycarbonyl; propoxycarbonyl; butoxycarbonyl;
pentyloxycarbonyl; cyclobutyloxycarbonyl;
cyclopentyloxycarbonyl; cyclohexyloxycarbonyl;
tetrahydro-2H-pyran-4-yloxycarbonyl;
cyclobutylmethoxycarbonyl;
tetrahydrofurfuryloxycarbonyl; benzyloxycarbonyl;
4-methoxybenzyloxycarbonyl; 3-methoxybenzyloxycarbonyl;

4-methylbenzyloxycarbonyl; 2-chlorobenzyloxycarbonyl;
3-chlorobenzyloxycarbonyl; 2-(phenyl)ethoxycarbonyl;
2-(4-methoxyphenyl)ethoxycarbonyl;
2-(4-chlorophenyl)ethoxycarbonyl,
2-(2-pyridyl)ethoxycarbonyl,
2-(4-methyl-5-thiazolyl)ethoxycarbonyl;
2-(2-thienyl)ethoxycarbonyl;
2-cyclohexylethoxycarbonyl; 2-methoxyethoxycarbonyl;
2-(methylthio)ethoxycarbonyl; 2-hydroxyethoxycarbonyl;
2-acetoxyethoxycarbonyl; 2-cyanoethoxycarbonyl;
2-(ethoxycarbonyl)ethoxycarbonyl;
2-(2-methoxyethoxy)ethoxycarbonyl;
3-oxobutoxycarbonyl; 2-(2-chlorophenyl)ethoxycarbonyl;
2-(3-methylphenyl)ethoxycarbonyl;
4,4,4-trifluorobutoxycarbonyl;
2-morpholinoethoxycarbonyl; 2-piperidinoethoxycarbonyl;
2-thiomorpholinoethoxycarbonyl;
1-methyl-2-morpholinoethoxycarbonyl;
3-morpholinopropoxycarbonyl;
3-(4-methyl-1-piperazinyl)propoxycarbonyl;
1-methyl-2-piperidylmethoxycarbonyl; acetyl; propionyl;
butyryl; pentanoyl; hexanoyl; cyclopropylcarbonyl;
cyclohexylcarbonyl; phenoxyacetyl; phenylacetyl;
3-methoxycarbonylpropionyl; carbamoyl;
3-oxapentamethylenecarbamoyl;
3-(2-acetoxyethyl)-3-azapentamethylenecarbamoyl;
methyl(2-morpholinoethyl)carbamoyl;
benzyl(methyl)carbamoyl;
methyl(3-pyridylmethyl)carbamoyl,
methyl(2-phenyl)ethylcarbamoyl;
2-cyanoethyl(methyl)carbamoyl; methyl(phenyl)carbamoyl;
ethyl(phenyl)carbamoyl;
2-phenoxyethoxycarbonyl; 1-benzylethoxycarbonyl;
3-(3-pyridyl)propoxycarbonyl;
2-[4-(N,N-dimethylamino)phenyl]ethoxycarbonyl;
2-phenylpropoxycarbonyl; 3-acetoxypropoxycarbonyl;
3-hydroxypropoxycarbonyl;

4-chlorophenyl(methyl)carbamoyl;
4-(2-acetoxy-ethyl)piperazinylcarbonyl;
4-(2-propionoxy-ethyl)piperazinylcarbonyl;
4-methoxycarbonylphenyl(methyl)carbamoyl;
2-(4-methoxyphenyl)propionyl; 4-chlorophenoxyacetyl;
cyclopentylacetyl; 2-(3-methylphenyl)propionyl;
2-methylphenoxyacetyl; 2-methylthiopropionyl;
methoxyacetyl.

In compounds of formula I, suitable substituents R_7 include the following:

Hydrogen; halo (fluoro, chloro, bromo), preferably fluoro or chloro, more preferably chloro; trifluoromethyl; C_{1-6} alkyl, preferably C_{1-4} alkyl (for example methyl, ethyl or propyl), more preferably methyl or ethyl, most preferably methyl; methoxy, $S(O)_mY_1$, in which R_1 is preferably C_{1-4} alkyl and m represents 0 or 1, (for example methylthio, ethylthio, propylthio, methylsulphinyl, ethylsulphinyl, propylsulphinyl) preferably m is 0, more preferably Y_1 is C_{1-2} alkyl, most preferably methyl.

In preferred compounds of formula I, R_8 represents hydrogen, fluoro, chloro or trifluoromethyl, more preferably hydrogen or chloro, and most preferably hydrogen.

In preferred compounds of formula I, R_8' represents hydrogen or chloro, especially hydrogen.

The substituents R_9 and R_{10} may be located at any position on the benz ring, namely in position 6-, 7-, 8- and/or 9- of the benz ring. Accordingly each of the substituents R_9 and R_{10} specified herein are considered to be named at each of these positions. In one group of compounds R_{10} is located at position 6- or 7- of the

benz ring, especially position 6-. In a preferred group of compounds R_{10} is located at position 8- or 9- of the benz ring, especially position 8-.

In preferred compounds of formula I, R_9 represents hydrogen, fluoro or chloro, more preferably hydrogen or fluoro, most preferably hydrogen.

In certain compounds of formula I, the group R_{10} may represent a carboxylic acyloxy group and may have the formula

$$-O.CO.R_{17}$$

in which R_{17} represents an alkyl group (e.g. C_{1-6}); an alkenyl group (e.g. C_{2-6}); a cycloalkyl group (e.g. C_{3-11}); a non-aromatic heterocyclic group; a carbocyclic aryl group or a heterocyclic aryl group; each of the groups being optionally substituted. In preferred compounds of formula I, R_{17} represents C_{1-6} alkyl; C_{2-6} alkenyl; C_{3-11} cycloalkyl; a 3-8 membered non-aromatic heterocyclic group; a carbocyclic aryl group; or a 5 or 6 membered heterocyclic aryl group; each of the groups being optionally substituted by Z. Preferably R_{17} represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, a 5-7 membered non-aromatic heterocyclic group containing one or two heteroatoms selected from oxygen, sulphur or nitrogen; phenyl; a 5 or 6 membered heterocylic aryl group containing one or two heteroatoms selected from oxygen, sulphur or nitrogen, each substituent R_{17} being optionally substituted by Z_1 or Z_2. Readily hydrolysable esters are included within the scope of the present invention as well as those which are less readily hydrolysable. Preferably R_{10} represents hydrogen, fluoro, chloro, bromo, trifluoromethyl, hydroxy, nitro, C_{1-6} alkyl (preferably C_{1-4} alkyl), C_{1-6} alkoxy (preferably C_{1-4} alkoxy) or a carboxylic acyloxy group as hereinabove

defined. More preferably R_{10} represents hydrogen, halo (preferably fluoro or chloro), hydroxy, C_{1-6} alkoxy (for example methoxy), C_{1-6} alkyl (for example methyl) or nitro or a carboxylic acyloxy group. Most preferably R_{10} represents hydrogen, fluoro, hydroxy or a carboxylic acyloxy group.

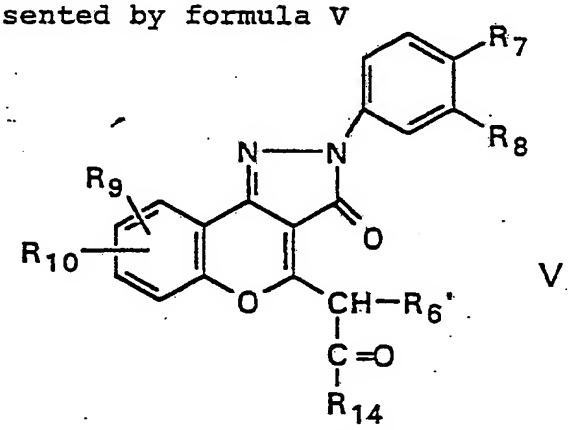
In particularly preferred compounds of formula I, R_{10} includes:
hydrogen; hydroxy; C_{3-10} cycloalkanoyloxy (for example cycloproylcarbonyl, cyclobutylcarbonyl or adamantylcarbonyloxy); C_{2-6} alkanoyloxy (for example acetoxy or propionyloxy) or C_{2-6} alkenoyloxy, both of which may be substituted with a substituent selected from C_{2-6} alkanoyloxy (for example acetoxy), $S(O)_mY_1$ (for example methylthio), C_{1-6} alkoxy (for example methoxy), carboxy, chloro, phenyl, di(C_{1-6})alkylamino or C_{2-6} alkoxycarbonyl (for example methoxycarbonyl or ethoxycarbonyl) and further optionally substituted by optionally substituted phenyl (for example 4-methoxyphenyl, 4-methylphenyl, 4-chlorophenyl); or R_{10} represents arylcarbonyloxy in which the aryl group is suitably phenyl, thienyl, furyl, pyridyl [which may themselves by substituted with C_{1-6} alkyl (for example methyl), C_{1-6} alkoxy (for example methoxy) or halo (for example chloro)].

Preferred are those in which R_{10} represents $OCO(CH_2)_pL$ in which p is 0-3 and L represents hydrogen, C_{3-11} cycloalkyl; di(C_{1-6}alkyl)amino; C_{2-6} alkanoyloxy; C_{2-6} alkoxycarbonyl, C_{1-6} alkylthio; C_{1-6} alkoxy; adamantyl or phenyl optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halo.

Preferred substituents R_{10} include chloroacetoxy; 4-chlorobenzoyloxy; cyclopentylcarbonyloxy; cyclohexylcarbonyloxy; hydrogen; fluoro; chloro;

hydroxy; acetoxy; propionyloxy; butyryloxy; pentanoyloxy; methoxycarbonylacetoxy; 3-methoxycarbonylpropionyloxy; acetoxyacetoxy; 3-(methylthio)propionyloxy; benzoyloxy; methoxyacetoxy; 4-methoxybenzyloxycarbonylacetoxy; ethoxycarbonylacetoxy; but-2-enoyloxy; 3-ethoxycarbonylpropionyloxy; carboxyacetoxy; adamantylcarbonyloxy; 3-phenylpropionyl; methylthioacetoxy; phenylacetoxy; dimethylaminoacetoxy; thenoyloxy; furoyloxy; 2-methylbenzoyloxy; 2-methoxybenzoyloxy; 4-methoxybenzoyloxy; pyridylcarbonyloxy; cyclopropylcarbonyloxy; cyclobutylcarbonyloxy; 4-methylbenzoyloxy; 3-methylbenzoyloxy.

A more preferred class of compounds of formula I are those represented by formula V

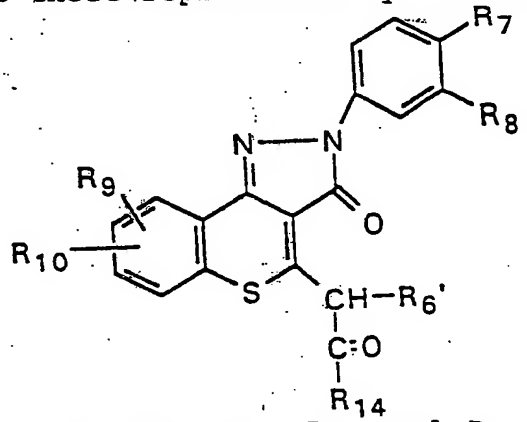


V

in which R_6', R_7, R_8, R_9, R_{10} and R_{14} and preferred substituents thereof are as recited in formula I above. More preferably, R_6' represents hydrogen, R_{14} represents OR_{15}, R_{16} or $NR_{12}R_{13}$ in which R_{12} represents methyl or ethyl, R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen, a 5 or 6 membered heterocyclic aryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur or nitrogen

or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or R_{12} and R_{13} together with nitrogen to which they are attached form a 3-8 membered non-aromatic heterocyclic ring which may contain a further heteroatom selected from oxygen, sulphur or nitrogen which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group; and R_{15} and R_{16}, which may be the same or different, represent optionally substituted groups selected from C_{1-6} alkyl; C_{2-6} alkenyl; C_{3-10} cycloalkyl; a 3-8 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen; phenyl; a 5 or 6 membered heterocyclic aryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur or nitrogen; R_9 represents hydrogen and R_{10} represents hydrogen, hydroxy, halo, C_{1-6} alkoxy or C_{1-6} alkyl.

A further more preferred class of compounds of formula I are those represented by formula VI

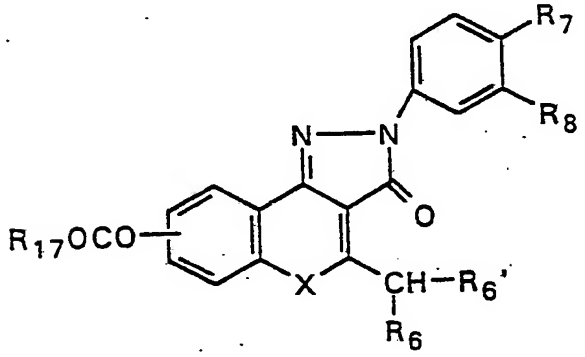


VI

in which $R_{6'}$, R_7, R_8, R_9, R_{10} and R_{14} and preferred substituents thereof, are as defined with respect to formula I above. More preferably, $R_{6'}$ represents hydrogen, R_{14} represents OR_{15}, R_{16} or $NR_{12}R_{13}$ in which R_{12} represents methyl or ethyl, R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen, a 5 or 6 membered heterocyclic aryl group

containing 1 to 3 heteroatoms selected from oxygen, sulphur or nitrogen or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or R_{12} and R_{13} together with nitrogen to which they are attached form a 3-8 membered non-aromatic heterocyclic ring which may contain a further heteroatom selected from oxygen, sulphur or nitrogen which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group; and R_{15} and R_{16}, which may be the same or different, represent optionally substituted groups selected from C_{1-6} alkyl; C_{2-6} alkenyl; C_{3-10} cycloalkyl; a 3-8 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen; phenyl; a 5 or 6 membered heterocyclic aryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur or nitrogen; R_9 represents hydrogen and R_{10} represents hydrogen, hydroxy, halo, C_{1-6} alkoxy or C_{1-6} alkyl.

A further more preferred class of compounds of formula I are those represented by formula VII

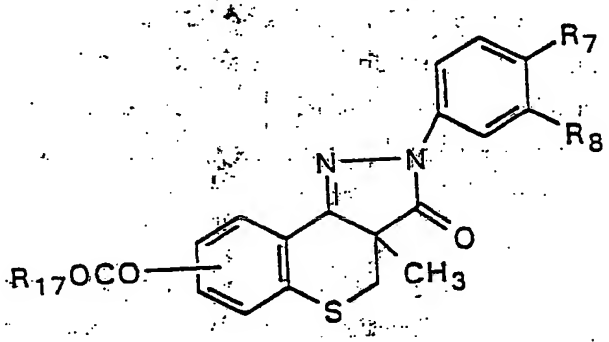


VII

in which R_6, R_6', R_7, R_8, and R_{17} and preferred substituents thereof are as defined with respect to formula I above. Preferably the substituent $O.CO.R_{17}$ is located in the 8-position or 9-position of the ring system, especially the 8-position. More preferably R_6' represents hydrogen and R_6 represents hydrogen, C_{2-6} alkoxycarbonyl or C_{1-6} alkylthio, R_{17} represents optionally substituted groups selected from C_{1-6} alkyl;

C_{2-6} alkenyl; C_{3-11} cycloalkyl; a 3-8 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen; phenyl; a 5 or 6 membered heterocyclic aryl group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen.

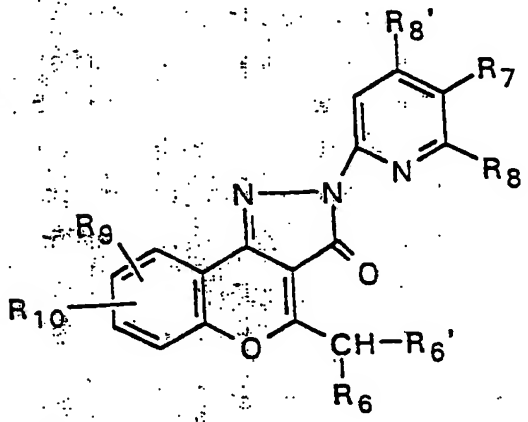
A further more preferred class of compounds of formula I are those represented by formula VIII



VIII

in which R_7, R_8 and R_{17} and preferred substituents thereof, are as defined with respect for formula I above. More preferably R_{17} represents optionally substituted groups selected from C_{1-6} alkyl; C_{2-6} alkenyl; C_{3-11} cycloalkyl; a 3-8 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen; phenyl; a 5 or 6 membered heterocyclic aryl group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen.

A further more preferred class of compounds of formula I are those represented by formula IX



IX

in which R_6, $R_{6'}$, R_7, R_8, $R_{8'}$, R_9 and R_{10} and preferred substituents thereof, are as defined with respect to formula I above. More preferably $R_{6'}$ represents hydrogen or methyl; R_6 represents hydrogen, halo, C_{2-6} alkanoyl, C_{2-6} alkoxycarbonyl, $S(O)_nY_1$, carbamoyl, carboxy or R_5 and R_6 together with a carbon atom to which they are attached represent cyclopropyl; R_7 represents hydrogen, halo, trifluoromethyl, methoxy, C_{1-6} alkyl, $S(O)_mY_1$; R_8 represents hydrogen, halo or trifluoromethyl; $R_{8'}$ represents hydrogen, halo or trifluoromethyl; R_9 and R_{10}, which may be the same or different, each represent halo; or R_9 represents hydrogen and R_{10} represents hydrogen, halo, trifluoromethyl, hydroxy, nitro, C_{2-6} alkanoyloxy, C_{1-6} alkyl or C_{1-6} alkoxy.

In one preferred group of compounds X represents oxygen. In a further preferred group of compounds R_6 represents COR_{14}, especially $COOR_{15}$, X preferably represents oxygen and Z preferably represents -CH=. In a further preferred group of compounds R_{10} represents $OCOR_{17}$, and X preferably represents oxygen and Z preferably represents -CH=.

Particular compounds of formula I are the compounds listed in Table A and pharmaceutically acceptable salts thereof provided in the specific Examples of the invention, including the free bases of compounds which have been exemplified as salts, hydrates or solvates.

Compounds of formula I may contain one or more chiral centres and exist in different optically active forms. When compounds of formula I contain one chiral centre the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers. The enantiomers may be

resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; formation of diastereoisomeric derivatives which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective derivatisation of one enantiomer by reaction with an enantiomer-specific reagent, for example enzymatic oxidation or reduction; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

For example, all compounds of formula IV have a chiral centre. In particular each [1]benzothiopyrano-[4,3-c]pyrazole having a 3a-methyl substituent listed in Table A (hereinafter) is hereby named as the R- or S- enantiomer. In addition the following named compound may also exist in the R- or S- enantiomeric form:

2-morpholinoethyl 2-(4-chlorophenyl)-3-oxo-1,2,3,4-tetrahydro[1]benzopyrano[4,3-c]pyrazole-4-acetate.

When compounds of formula I contain more than one chiral centre, the compounds may exist in diastereoisomeric forms. The present invention includes each diastereoisomer and mixtures of the diastereoisomers. The diastereoisomers may be separated by methods known to those skilled in the art, for example by crystallisation or liquid chromatography.

Certain compounds of formula I may exist in different tautomeric forms or as different geometric isomers.

Some compounds of formula I are bases and may form acid addition salts with inorganic or organic acids, for example hydrochloric acid, hydrobromic acid, fumaric acid, tartaric acid and citric acid. It will be appreciated that such salts, provided they are pharmaceutically acceptable, may be used in therapy in place of the corresponding compounds of formula I. Such salts may be prepared for example by reacting the compound of formula I with a suitable acid in a conventional manner.

Certain compounds of formula I may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

Certain compounds of formula I may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

The present invention also includes pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I together with a pharmaceutically acceptable diluent or carrier.

As used hereinafter, the term "active compound" denotes a [1]benzopyrano[4,3-c]pyrazole or a [1]benzothiopyrano[4,3-c]pyrazole of formula I. In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally or topically. Thus the therapeutic compositions of the present invention take the form of any of the known pharmaceutical

compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1-90% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art.

Compositions for oral administration are preferred compositions of the invention and these are known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oily suspensions. Tablets may be prepared by mixing the active compound with an inert diluent such as lactose or calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 0.1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the

present invention in a suitable vegetable oil, for example arachis oil.

Compositions for topical administration are also preferred compositions of the invention. The pharmaceutically active compound may be dispersed in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating the active compound in a topical vehicle such as petrolatum and/or light liquid paraffin, dispersed in an aqueous medium using surfactants. An ointment may be prepared by mixing the active compound with a topical vehicle such as a mineral oil, petrolatum and/or a wax e.g. paraffin wax or beeswax. A gel may be prepared by mixing the active compound with a topical vehicle comprising a gelling agent e.g. basified Carbomer BP, in the presence of water. Topically administrable compositions may also comprise a matrix in which the pharmaceutically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as described above, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol.

Compositions of the invention suitable for rectal administration are known pharmaceutical forms for such administration, for example suppositories with semi-synthetic glycerides or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are known pharmaceutical forms for such administration, for example sterile

suspensions in aqueous and oily media or sterile solutions in a suitable solvent.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The compounds of formula I are indicated for use as immunomodulatory agents, and are generally immunosuppressants, but some compounds, in certain disease states, may exhibit immunostimulant activity. The compounds according to the invention are useful in the treatment of diseases resulting from an aberrant immune reaction. Thus the pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I may be used to treat diseases with an immunological association for example tissue rejection, such as kidney rejection; autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus; cutaneous disorders, such as contact sensitivity, eczema and psoriasis; and neoplasia, such as melanoma.

In such treatment the amount of the compound of formula I administered per day will be such as to give a therapeutic effect and is generally in the range 0.1 to 2000 mg, preferably 1 to 500 mg.

Accordingly, in another aspect, the present invention also includes a method of treating diseases with an immunological association, comprising the

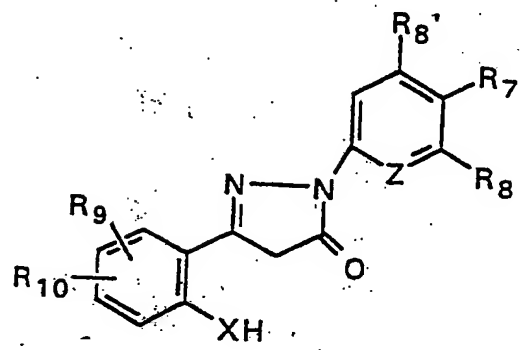
administration of a therapeutically effective amount of a compound of formula I.

The therapeutic activity of compounds of formula I has been demonstrated by means of tests on standard laboratory animals. Such tests include, for example, the oral and parenteral administration of the compounds to BALB/c mice. Thus, compounds of formula I are useful as immunomodulatory agents. Whilst the precise amount of active compound administered will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history and always lies within the sound discretion of the administering physician, a suitable dose for oral administration to mammals, including humans, is generally within the range 0.01-40 mg/kg/day, more usually 0.2-25 mg/kg/day given in single or divided doses. For parenteral administration, a suitable dose is generally within the range 0.001-4.0 mg/kg/day, more usually 0.005-1 mg/kg/day given in single or divided doses or by continuous infusion. A suitable preparation for topical administration generally contains the active ingredient within the range 0.01-20% by weight, more usually 0.05-5% by weight. Oral administration is preferred.

Processes for the preparation of compounds of formula I will now be described. These processes form a further aspect of the present invention.

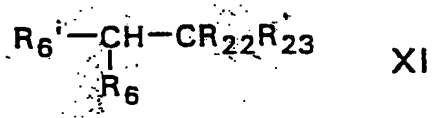
Compounds of formula I which are represented by formula II may be prepared by oxidising compounds of formula I which are represented by formula III, for example by reaction with chloranil.

Compounds of formula I which are represented by formula II may be prepared by reacting compounds of formula X,



X

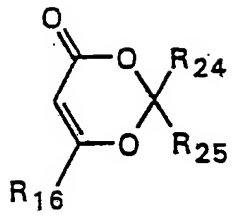
or a tautomer thereof, with compounds of formula XI



XI

in which R_{22} represents $(OQ)_2$ and R_{23} represents OQ or NQ'_2; or R_{22} represents $(SQ)_2$ and R_{23} represents SQ or NQ'_2; or R_{22} represents =NH and R_{23} represents OQ or SQ; or R_{22} represents =O and R_{23} represents a leaving group for example an optionally substituted 1-imidazolyl group, in which Q and Q' represent a C_{1-4} alkyl group or a benzyl group, for example by heating at 50-200°C.

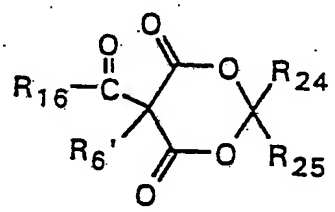
Compounds of formula I which are represented by formula II in which $R_{6'}$ represents hydrogen and R_6 represents a carboxylic acyl group may be prepared by reacting compounds of formula X with compounds of formula XIIa



XIIa

or a tautomer thereof, in which R_{24} and R_{25} may be the same or different, and each represent a C_{1-6} alkyl group or a benzyl group, for example by heating in an organic liquid for example xylene at a temperature between 50-200°C.

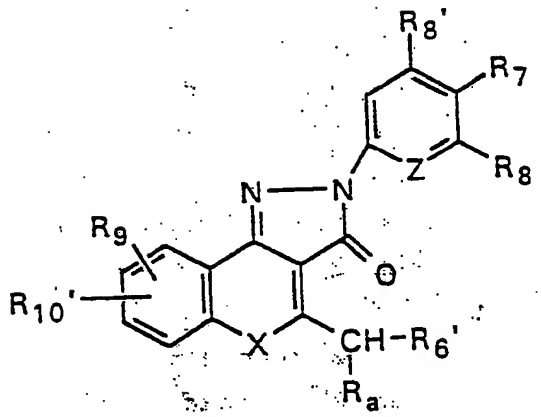
Compounds of formula I which are represented by compounds of formula II in which R_6 represents a carboxylic acyl group may be prepared by reacting compounds of formula X with compounds of formula XIIb



XIIb

or a tautomer thereof, in which R_{24} and R_{25} may be the same or different and each represents a C_{1-6} alkyl group or a benzyl group, for example by heating in an organic liquid, for example xylene at a temperature between 50 and 250°C.

Compounds of formula I which are represented by compounds of formula II in which R_6 represents a group $CONR_{12}R_{13}$ or an esterified carboxyl group may be prepared by reacting compounds of formula II'



II'

in which $R_{10'}$ represents R_{10} and R_a represents COA, where A represents a leaving group, for example hydroxyl, halo, C_1-C_6 alkoxy, aryloxy, arylmethoxy, C_1-C_6 acyloxy or C_{1-6} alkoxycarbonyloxy with an amine of formula $NHR_{12}R_{13}$ or an alcohol, for example of formula $R_{15}OH$ respectively, for example at 0-250°C, optionally in the presence of an organic liquid which is preferably a solvent for the reactants and optionally in the presence of a catalyst for the reaction.

Compounds of formula I which are represented by compounds of formula II in which R_6 represents a group which is substituted by a carboxylic acyloxy group may be prepared by acylation of corresponding compounds of formula II substituted by a hydroxy group, for example by reaction with an acyl halide.

Compounds of formula I which are represented by compounds of formula II in which R_6 represents a group which is substituted by a hydroxyl group may be prepared from corresponding compounds of formula I substituted with a carboxylic acyloxy group, for example acetoxy, by hydrolysis.

Compounds of formula I which are represented by compounds of formula II in which R_{10} represents a carboxylic acyloxy group may be prepared by acylating

compounds of formula II' in which R_a represents R_6 and $R_{10'}$ represents a hydroxy group by reaction with an acylating agent. The acylation reaction may be carried out by reacting the compound of formula II' with an acyl halide e.g. $R_{17}COCl$ or an acid anhydride $(R_{17}CO)_2O$ in the presence of a base at a temperature in the range -10°C to 40°C. The acylation reaction may also be carried out by reacting the compound of formula II' with a carboxylic acid $R_{17}COOH$ in the presence of a dehydrating agent, for example dicyclohexylcarbodiimide, preferably in the presence of a base e.g. pyridine. Compounds of formula II' in which $R_{10'}$ represents hydroxy may be prepared by reacting compounds of formula II' in which $R_{10'}$ represents a C_{1-6} alkoxy group with a Lewis acid, for example aluminium chloride or boron tribromide.

Compounds of formula I which are represented by formula II in which R_6 and R_6' both represent hydrogen may be prepared by decarboxylating compounds of formula II in which $R_{6'}$ represents hydrogen and R_6 represents carboxyl, or by hydrolysing compounds of formula II in which R_6' represents hydrogen and R_6 represents a group which may be hydrolysed to a carboxyl group such as a C_{2-6} alkoxycarbonyl group or carbamoyl, for example by reaction with sulphuric acid, followed by decarboxylation.

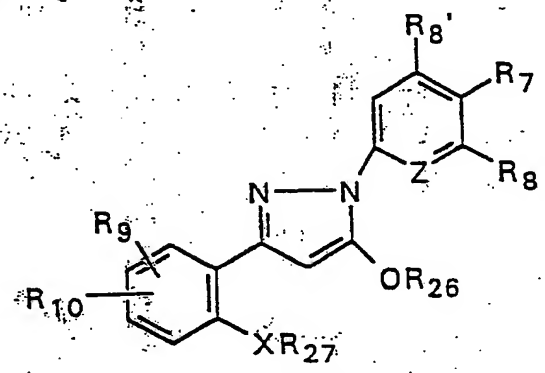
Compounds of formula I which are represented by formula II in which R_6 represents a C_{1-6} alkylsulphinyl group or a C_{1-6} alkylsulphonyl group may be prepared by oxidation of compounds of formula II in which R_6 represents a C_{1-6} alkylthio group with, for example, 3-chloroperoxybenzoic acid.

Compounds of formula I which are represented by compounds of formula II in which R_6 represents a

carboxyl group may be prepared from compounds of formula II in which R_6 represents 4-methoxybenzyloxycarbonyl for example by treatment with trifluoroacetic acid and anisole in a solvent, for example dichloromethane.

Compounds of formula I which are represented by compounds of formula II in which R_{10} represents a carboxyalkylcarbonyloxy group for example carboxyacetoxy, may be prepared from compounds of formula II in which R_{10} represents 4-methoxybenzyloxycarbonylalkylcarbonyloxy, for example 4-methoxybenzyloxycarbonylacetoxy, by treatment with trifluoroacetic acid and anisole in a solvent, for example dichloromethane.

Compounds of formula I which are represented by formula II may be prepared by reacting compounds of formula XIII

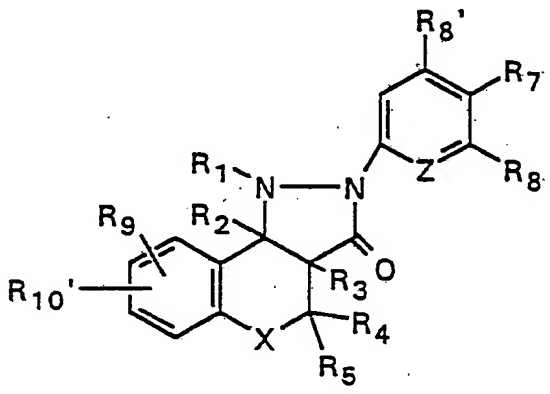


XIII

in which R_{26}' represents hydrogen, or a tautomer thereof, or in which R_{26} represents a group COR_{28} wherein R_{28} represents hydrogen, an optionally substituted C_{1-4} alkyl group or a benzyl group and R_{27} represents $COCHR_6R_{6'}$, with a base e.g. piperidine in a suitable solvent e.g. ethanol.

Compounds of formula I which are represented by formula III may be prepared by reducing compounds of formula I which are represented by formula II, for example by reaction with sodium borohydride.

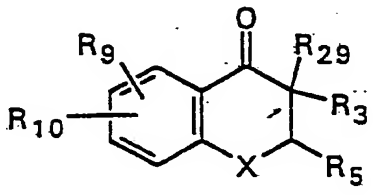
Compounds of formula I which are represented by formula III or IV may be prepared from the corresponding compounds of formula I'



I'

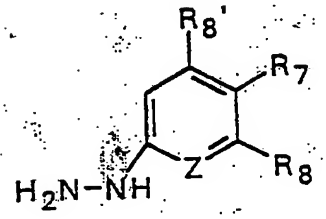
in a similar manner as compounds of formula II are prepared from compounds of formula II'.

Compounds of formula I which are represented by formula III may be prepared by reacting compounds of formula XIV



XIV

in which R_3 represents hydrogen, R_5 represents $CHR_6R_{6'}$, R_{29} represents $COOR_{30}$ or carbamoyl and R_{30} represents a C_{1-4} alkyl group or a benzyl group with a hydrazine of formula XV



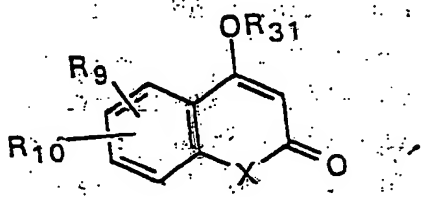
XV

for example, by heating at 50-250°, for example in acetate acid or in an inert organic liquid containing an acid catalyst, e.g. xylene containing p-toluene sulphonic acid.

Compounds of formula I which are represented by formula IV may be prepared by reacting compounds of formula XIV in which X represents S, R_3 represents methyl, R_5 represents hydrogen and R_{29} and R_{30} are as defined, with compounds of formula XV in which Z represents -CH=.

Compounds of formula I which are represented by formulae V to IX may be prepared as described with reference to the preparation of compounds of formulae II to IV above.

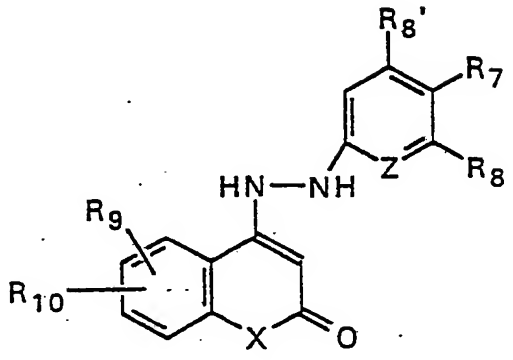
Compounds of formula X may be prepared by reacting compounds of formula XVI



XVI

in which R_{31} represents hydrogen, a C_{1-4} alkyl group or a benzyl group with a hydrazine of formula XV, for example by heating at 50-200°C in an organic liquid for example toluene. Preferably the compound of formula XVI is used in excess of the stoichiometric amount.

Compounds of formula X may be prepared by reacting compounds of formula XVII



XVII

with an acid, for example hydrochloric acid, or with a base, for example a solution of sodium hydroxide.

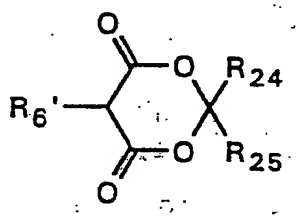
Compounds of formula X in which R_{10} represents a hydroxyl group may be prepared by reacting compounds of formula X in which R_{10} represents a C_{1-6} alkoxy group with a Lewis acid, for example aluminium chloride or boron tribromide.

Compounds of formula XI in which R_{22} represents $(OQ)_2$ and R_{23} represents OQ may be prepared for example a) by reacting compounds of formula R_6,R_6CH-CX_3 in which X is halo with a sodium alkoxide of formula NaOQ in which Q is a C_{1-4} alkyl group or a benzyl group, or b) by reacting compounds of formula R_6,R_6CH-CN with an alcohol of formula QOH in the presence of an anhydrous acid, for example hydrogen chloride, to give compounds of formula $R_6,R_6CH-C(=NH)OQ$ as their acid salts, e.g. hydrochloride salts, which are then reacted with further alcohol of formula QOH.

Compounds of formula XI in which R_{22} represents $(SQ)_2$ and R_{23} represents SQ may be prepared for example from compounds of formula $R_6,R_6CH-COCl$ by reaction with thiols of formula QSH in which Q represents a C_{1-4} alkyl group or a benzyl group in the presence of a Lewis acid, for example zinc chloride.

Other compounds of formula XI may be prepared by methods known to those skilled in the art.

Compounds of formula XIIb or tautomers thereof may be prepared by the acylation of compounds of formula XIX



XIX

by reaction with an acyl chloride R_{16}-COCl, for example in the presence of pyridine in an inert solvent at a temperature in the range -10°C to 50°C.

Compounds of formula XIII in which R_{26} represents COR_{28} and R_{27} represents $COCHR_6R_6$, may be prepared by acylation of compounds of formula XIII in which R_{26} represents COR_{28} and R_{27} represents hydrogen, for example by reaction with an acid anhydride of formula $(R_6,R_6CHCO)_2O$ or an acid halide e.g. of formula $R_6,R_6CHCOCl$.

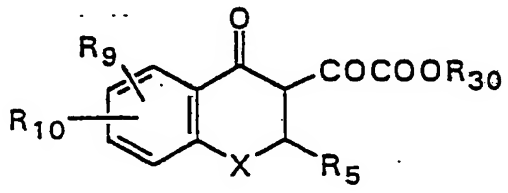
Compounds of formula XIII in which R_{26} represents COR_{28} and R_{27} represents hydrogen may be prepared by the acylation of compounds of formula X for example by

reaction with an acid anhydride of formula $(R_{28}CO)_2O$ in the presence of a salt (e.g. the sodium salt) of the corresponding acid.

Compounds of formula XIII in which R_{26} and R_{27} are identical and represent $COCHR_6,R_6$, may be prepared by acylation of compounds of formula X for example by using an acid anhydride of formula $(R_6,R_6CHCO)_2O$ in the presence of a salt (e.g. the sodium salt) of the corresponding acid.

Compounds of formula XIII in which R_{27} represents $COCHR_6R_6$, and R_{26} represents hydrogen, or tautomers thereof, may be prepared by reacting a compound of formula XIII in which R_{26} represents COR_{28} and R_{27} represents $COCHR_6R_6$, with a base e.g. piperidine in a suitable solvent e.g. ethanol.

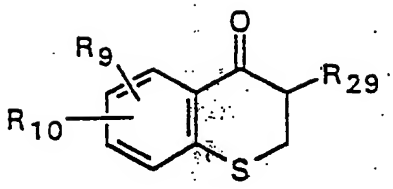
Compounds of formula XIV in which R_{29} represents $COOR_{30}$ and R_5 represents CHR_6R_6, may be prepared by heating compounds of formula XX



XX

in which R_{30} represents a C_{1-4} alkyl group or a benzyl group, for example with glass powder or glass wool.

Compounds of formula XIV in which R_3 represents methyl and R_5 represents hydrogen may be prepared by reacting compounds of formula XVIII



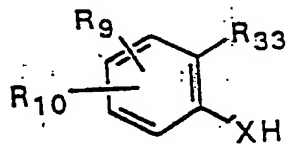
XVIII

with a methylating agent for example a methyl halide, for example methyl iodide in the presence of a base, for example a sodium alkoxide e.g. sodium methoxide.

Compounds of formula XIV in which R_{29} represents carbamoyl may be prepared from compounds of formula XIV in which R_{29} represents cyano by methods known to those skilled in the art.

Compounds of formula XV may be made by methods known to those skilled in the art.

Compounds of formula XVI in which R_{31} represents hydrogen may be prepared by reacting compounds of formula XXI



XXI

in which R_{33} represents hydrogen with malonic acid in the presence of an acid chloride e.g. phosphoryl chloride and a Lewis acid e.g. zinc chloride.

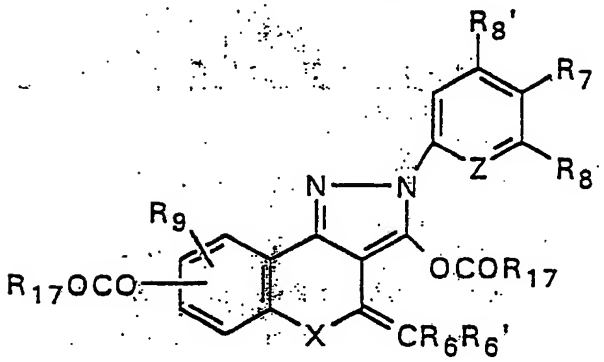
Compounds of formula XVI in which R_{31} represents hydrogen may be prepared by reacting compounds of formula XXI in which R_{33} represents a group COR_{34} in which R_{34} represents a C_{1-5} alkyl group, with a base, for example sodium hydride, followed by treatment with a dialkyl carbonate of formula $(QO)_2CO$ in which Q represents a C_{1-4} alkyl group or a benzyl group, e.g. dimethyl carbonate.

Compounds of formula XVI in which R_{31} represents a C_{1-4} alkyl group or a benzyl group may be prepared by base catalysed alkylation or benzylation of compounds of formula XVI in which R_{31} represents hydrogen for example by reaction with an alkyl halide or a benzyl halide.

Compounds of formula XVII may be prepared by reacting compounds of formula XVI with a hydrazine of formula XV for example by heating at 50-200°C in a suitable solvent for example toluene. In cases where a mixture of compounds of formula X and XVII are obtained, these compounds may be separated by virtue of their different solubilities in an organic liquid for example dichloromethane.

Compounds of formula XVIII to XXI may be prepared by methods known to those skilled in the art.

Compounds of formula I which are represented by formula II in which R_{10} represents $R_{17}OC.O$ may be prepared by acylation of compounds of formula II in which R_{10} represents a hydroxyl group. During the acylation reaction there may be formed compounds of formula XXII



XXII

which may be hydrolysed, for example on exposure to atmospheric moisture to the desired compounds of formula II mentioned above.

Certain intermediate compounds of formulae X, XI, XII a) and b), XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, and XXII are believed to be novel compounds. All novel compounds herein are claimed as a further aspect of the invention.

The invention is illustrated by the following non-limitative Examples. In the Examples parts and percentages are by weight and compositions of mixed solvents are given by volume. Characterisation was by elemental analysis and one or more of the following spectroscopic techniques: nuclear magnetic resonance, infra-red and mass spectroscopy.

Preparation of Novel Compounds of Formula XVI

Example 1

A mixture of 5'-fluoro-2'-hydroxyacetophenone (10 g) in dry toluene (130 ml) was added dropwise over 20 minutes to a stirred suspension of sodium hydride (6.2 g; 60% dispersion in mineral oil) in dry toluene (130 ml) which was boiling under reflux under nitrogen. After boiling for a further 10 minutes heating was continued while a solution of diethyl carbonate (15.7 ml) in dry toluene (130 ml) was added dropwise over 25 minutes. This mixture was stirred and heated under reflux for 4 hours. On cooling, the reaction mixture was poured on to iced 2M hydrochloric acid (700 ml). The solid obtained was collected by filtration and then dissolved in 4M aqueous sodium hydroxide (325 ml). This solution was washed with ether and then acidified with 5M hydrochloric acid. The solid obtained was collected by filtration, washed with water and dried to give 6-fluoro-4-hydroxycoumarin, m.p. 250-251°C.

Preparation of Novel Compounds of Formula XIV

Example 2

a) Dimethyl oxalate (1.4 g) was added to a stirred solution of sodium (0.3 g) in methanol (10 ml) with warming to aid dissolution. The solution was cooled to ambient temperature and a solution of 6-methoxy-4-thiochromanone (1.2 g) in methanol (6 ml) was added dropwise over 15 minutes. The mixture was stirred at ambient temperature for 3 hours and then allowed to stand for 4 days. The solvent was removed under reduced pressure and the residue partitioned between water and toluene. The aqueous layer was basified with

2M sodium hydroxide solution, separated and acidified with 2M hydrochloric acid. The solid formed was collected by filtration and recrystallised from methanol to give methyl 6-methoxy-4-oxo-3-thiochroman-glyoxylate, m.p. 85-89°C.

b) A mixture of methyl 6-methoxy-4-oxo-3-thiochroman-glyoxylate (6.2 g) and glass powder (2.8 g) was heated with stirring at 180°C for 30 minutes. The mixture was cooled to ambient temperature, extracted with boiling acetone and filtered. The filtrate was evaporated and the residue was taken up in hot propan-2-ol then hot filtered from some tar. The filtrate was cooled and filtered to give methyl 6-methoxy-4-oxo-3-thiochroman-carboxylate, m.p. 61-65°C.

c) A solution of methyl 6-methoxy-4-oxo-3-thiochromancarboxylate (1.0 g) in toluene (10 ml) was added to a solution of sodium (0.4 g) in dry methanol (15 ml) with stirring. The mixture was boiled under reflux for 10 minutes then cooled to ambient temperature and methyl iodide (1 ml) added. The mixture was boiled under reflux, with stirring, for 3 hours then left at ambient temperature for 18 hours. The mixture was neutralised with glacial acetic acid then evaporated under reduced pressure. The residue was added to water and extracted with toluene. The combined toluene extracts were washed with saturated sodium bicarbonate solution, then water, dried and evaporated under reduced pressure. The residue was separated by flash chromatography on silica using ethyl acetate/petroleum ether (b.p. 60-80°C, 1:4) as the mobile phase. The solid obtained was recrystallised from ethyl acetate/petroleum ether (b.p. 60-80°C) to give methyl 6-methoxy-3-methyl-4-oxo-3-thiochromancarboxylate, m.p. 66-73°C.

Example 3

a) A stirred mixture of 4-methoxythiophenol (20 g), diethyl ethoxymethylene malonate (29.3 ml) and potassium hydrogen sulphate (0.4 g) was heated at 160-170°C for 2 hours. Polyphosphoric acid (152 g) was added to the reaction mixture with heating at 80-90°C for 1 hour. The reaction mixture was poured into water, extracted with ether and the ether extracts combined and dried. Following removal of the solvent the solid obtained was recrystallised from ethyl acetate/petroleum ether (b.p. 60-80°C) to give ethyl 6-methoxy-4-oxo-4-H-thiochromene-3-carboxylate, m.p. 102-104°C.

b) Copper chloride (150 mg) was added to a stirred mixture of ethyl 6-methoxy-4-oxo-4-H-thiochromene-3-carboxylate (4 g) in tetrahydrofuran (40 ml) under nitrogen at -78°C. A 3M solution of methylmagnesium bromide in ether (5 ml) was added slowly maintaining the temperature below -65°C and then the reaction mixture was allowed to warm to ambient temperature. The reaction mixture was poured into ether/2M hydrochloric acid, the aqueous layer extracted with ether, and the combined ether layers dried to give the crude product. Purification by flash chromatography over silica using 1% methanol/dichloromethane as the mobile phase gave ethyl 6-methoxy-2-methyl-4-oxo-3-thiochromancarboxylate as an oil.

Preparation of Novel Compounds of Formula XIIb

Example 4

Pyridine (12 g) was added dropwise over 3-5 minutes to a stirred solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (20 g) in dichloromethane (220 ml) at

0°C. The resulting solution was stirred at 0°C for 10 minutes and then while the temperature was maintained at 0-2°C 3-methoxycarbonylpropionyl chloride (22.8 g) was added dropwise. After the addition the mixture was stirred at 0°C for 60 minutes, then allowed to warm up to ambient temperature and kept at this temperature for 18 hours. The mixture was washed with 1M hydrochloric acid, then water, dried and evaporated to give methyl 4-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-oxobutyrate as a viscous oil.

Examples 5-15

In a similar manner to that described in Example 4, a compound of formula XIIb was prepared by reacting 2,2-dimethyl-1,3-dioxane-4,6-dione (XIX) with $R_{16}COCl$ (in which R_{16} is as defined), as summarised in Table 1 below.

Table 1

Ex	R_{16}	Amounts of Reactants: XIX (g)	$R_{16}COCl$ (g)	Pyridine (g)	Dichloromethane (ml)	m.p. of XIIb (°C)	Notes
5	CH_2Ph	10.0	11.6	12.0	120	-	(1)
6	CH_2OPh	10.0	11.2	12.0	120	-	(1)
7	cyclohexyl	10.0	11.0	12.0	120	-	(1)
8	cyclopropyl	10.0	7.8	12.0	120	-	(1)
9	4-methoxyphenethyl	13.7	18.8	16.1ml	210	-	(1)
10	4-chlorophenoxymethyl	10.0	11.9ml	12.3ml	132	115-116	(2)
11	3-methylphenethyl	14.0	17.7	16.5ml	200	-	(6)
12	cyclopentylmethyl	11.0	13.4	13.3	280	-	(4) (3) (1)
13	2-methylphenoxymethyl	10.0	15.0	12.0	250	88-90	(5)
14	2-methylthioethyl	20.0	21.2	24.6ml	290	-	(1) (6)
15	methoxymethyl	10.0	8.1	12.0	120	-	

Notes

(1) Product was a viscous oil.

(2) After washing with hydrochloric acid and water, the solid product was collected by filtration.

(3) The reaction was carried out under nitrogen.

(4) The crude product was purified by flash chromatography using dichloromethane as the mobile phase.

(5) The crude product was purified by trituration with hot industrial methylated spirit and the solid product collected by evaporation.

(6) After washing with hydrochloric acid and water the solvent was removed to leave a dark solid.

The compounds prepared in the above Examples were as follows:

5 2,2-dimethyl-5-phenylacetyl-1,3-dioxane-4,6-dione

6 2,2-dimethyl-5-phenoxyacetyl-1,3-dioxane-4,6-dione

7 5-cyclohexylcarbonyl-2,2-dimethyl-1,3-dioxane-4,6-dione

8 5-cyclopropylcarbonyl-2,2-dimethyl-1,3-dioxane-4,6-dione

9 2,2-dimethyl-5-[3-(4-methoxyphenyl)propionyl]-1,3-dioxane-4,6-dione

10 5-(4-chlorophenoxyacetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione

11 2,2-dimethyl-5-[3-(3-methylphenyl)propionyl]-1,3-dioxane-4,6-dione

12 5-(2-cyclopentyl-1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione

13 5-[1-hydroxy-2-(2-methylphenoxy)ethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione

14 2,2-dimethyl-5-(3-methylthiopropionyl)-1,3-dioxane-4,6-dione

15 5-methoxyacetyl-2,2-dimethyl-1,3-dioxane-4,6-dione

Preparation of Novel Compounds of Formula XI

Example 16

A stirred mixture of propyl cyanoacetate (30.5 g), dry propanol (18.5 g) and dry ether (134 ml) was saturated with hydrogen chloride at 0-5°C. The mixture was allowed to warm to ambient temperature and kept at this temperature for 66 hours. After evaporation under reduced pressure, the residual oil obtained was stirred and heated at 45-50°C in dry propanol (180 ml) for 24 hours. After cooling to ambient temperature, dry ether (200 ml) was added and the mixture filtered. The filtrate was evaporated under reduced pressure to give an oil which was distilled under reduced pressure to give tripropyl ortho(propoxycarbonyl)acetate, b.p. 165-175°C (5 mm Hg).

Example 17

(a) A stirred mixture of isopropyl cyanoacetate (15.0 g) and dry methanol (4.2 g) was saturated with hydrogen chloride at 0-5°C. Dry ether (70 ml) was added to the reaction mixture and the solid product collected by filtration and washed with ether to give methyl isopropoxycarbonylacetimidate hydrochloride.

(b) A mixture of methyl isopropoxycarbonylacetimidate hydrochloride (17 g) and dry methanol (52.7 ml) was stirred for 30 minutes. Dry ether (290 ml) was added and the mixture stirred and heated under reflux for 18 hours. The reaction mixture was cooled to 0°C, filtered and the filtrate washed with 10% sodium carbonate solution (300 ml) saturated sodium carbonate solution (50 ml), dried and evaporated under reduced pressure to give trimethyl ortho(isopropoxycarbonyl) acetate as an oil.

Example 18

a) A solution of methylthioacetonitrile (100 g) and methanol (47 ml) in dry ether (644 ml) was saturated with hydrogen chloride at 0-5°C. The mixture was allowed to warm to ambient temperature during 16 hours. The resulting solid product was collected by filtration, washed and dried to give methyl methylthioacetimidate hydrochloride as a sticky solid.

b) A mixture of the methyl methylthioacetimidate hydrochloride and methanol (551 ml) was stirred at 35-45°C for three hours and then left at ambient temperature for 72 hours. The mixture was then filtered and the filtrate evaporated to give an oil containing a little solid which was removed by filtration through cotton wool giving trimethyl ortho(methylthio)acetate as an oil, b.p. 96-104°C (5 mm Hg).

Preparation of Novel Compounds of Formula X

Example 19

a) A stirred mixture of 4-hydroxy-5-methoxy-coumarin (6.5 g), 4-chlorophenylhydrazine (7.3 g) and dry toluene (66 ml) was heated under reflux with removal of the water formed in the reaction. On cooling, the solid obtained was collected by filtration to give 4-[2-(4-chlorophenyl)hydrazino]-5-methoxy-coumarin, m.p. 206-209°C.

b) A mixture of 4-[2-(4-chlorophenyl)hydrazino]-5-methoxycoumarin (1.6 g), 5M aqueous sodium hydroxide (1 ml) and industrial methylated spirit (100 ml) was boiled under reflux for 4 hours. On cooling, the mixture was filtered. The filtrate was evaporated to dryness and the residue was partitioned between dichloromethane and water. The dichloromethane layer was separated off, dried and concentrated to give after filtration, 1-(4-chlorophenyl)-3-(2-hydroxy-6-methoxyphenyl)-2-pyrazolin-5-one, m.p. 185-188°C.

Example 20

a) A stirred mixture of 4-hydroxy-6-methoxy-coumarin (9.2 g) and 4-chlorophenylhydrazine (10.2 g) in dry toluene (82 ml) was heated under reflux for 5.5 hours with removal of the water produced in the reaction. More 4-chlorophenylhydrazine (5.0 g) was added and the mixture heated under reflux for a further 2 hours. The mixture was allowed to cool to ambient temperature and the solid formed collected by filtration to give 1-(4-chlorophenyl)-3-(2-hydroxy-5-methoxyphenyl)-2-pyrazolin-5-one, m.p. 197-203°C.

b) 1-(4-Chlorophenyl)-3-(2-hydroxy-5-methoxyphenyl)-2-pyrazolin-5-one (5.5 g), aluminium chloride (9.35 g) and dry xylene (66 ml) were stirred and heated at 100°C for 1 hour. On cooling, the xylene was decanted off and a mixture of 2M hydrochloric acid (90 ml) and ice (200 g) added to the residue. After trituration the solid formed was collected by filtration, dried and then recrystallised from methanol to give 1-(4-chlorophenyl)-3-(2,5-dihydroxyphenyl)-2-pyrazolin-5-one, m.p. 220-225°C (with decomposition).

Example 21

a) A stirred mixture of 4-hydroxy-6-methoxycoumarin (10.0 g), 4-trifluoromethylphenylhydrazine (22.9 g), dry toluene (375 ml) and p-toluenesulphonic acid (0.2 g) was refluxed for a total of 25 hours (with intermittent storage at ambient temperature for a total of 130 hours) during which a further portion of p-toluenesulphonic acid (0.2 g) was added after refluxing for 7.5 hours, and then further 4-trifluoromethylphenylhydrazine (5 g) and p-toluenesulphonic acid (0.2 g) added after refluxing for 13 hours. After cooling to ambient temperature, the reaction mixture was filtered and the solid recrystallised from acetonitrile with hot filtration. The solid collected was boiled with dichloromethane and hot filtered to give crude 6-methoxy-4-[2-(4-trifluoromethylphenyl)-hydrazino] coumarin.

b) A mixture of crude 6-methoxy-4-[2-(4-trifluoromethylphenyl)hydrazino]coumarin (8.5 g), 5M hydrochloric acid (8.5 ml) and industrial methylated spirit (82 ml) was stirred and boiled under reflux for 29 hours. On cooling, the solid obtained was collected by filtration to give 3-(2-hydroxy-5-methoxyphenyl)-1-(4-

trifluoromethylphenyl)-2-pyrazolin-5-one, m.p. 212-216°C.

c) A stirred mixture of 3-(2-hydroxy-5-methoxyphenyl)-1-(trifluoromethylphenyl)-2-pyrazolin-5-one (2.0 g) and aqueous hydrobromic acid (48%, 200 ml) was refluxed for two hours. The reaction mixture was hot filtered and the solid collected recrystallised from aqueous industrial methylated spirit to give 1-(4-trifluoromethylphenyl)-3-(2,5-dihydroxyphenyl)-2-pyrazolinone, m.p. 253-257°C.

Example 22

a) A stirred mixture of 4-hydroxy-6-methoxy coumarin (17.1 g), 4-bromophenylhydrazine (25.0 g) and dry toluene (160 ml) was refluxed for 3 hours. A further portion of the hydrazine (25.0 g) was added and refluxing was continued for a further 3 hours. The reaction mixture was cooled to ambient temperature and the solid collected after filtration digested with boiling dichloromethane and then hot filtered. The filtrate was concentrated, cooled and filtered to give 1-(4-bromophenyl)-3-(2-hydroxy-5-methoxyphenyl)-2-pyrazolin-5-one, m.p. 197-200°C.

b) A stirred mixture of 1-(4-bromophenyl)-3-(2-hydroxy-5-methoxyphenyl)-2-pyrazolin-5-one (5.4 g), aluminium chloride (8.2 g) and dry xylene (60 ml) was heated on a steam bath for 5 hours, then cooled to ambient temperature and kept at this temperature for 18 hours. The xylene was decanted away to leave a gum which was treated with dilute hydrochloric acid (117 ml) and ice. The solidified gum was collected by filtration and washed with water and petroleum ether (b.p. 60-80°C). The crude product was purified by flash chromotography on silica using toluene/acetic

acid (9:1) as the mobile phase. The appropriate fractions were combined, washed, dried and evaporated to give a solid which was recrystallised from aqueous industrial methylated spirit to give 1-(4-bromophenyl)-3-(2,5-dihydroxyphenyl)-2-pyrazolin-5-one, m.p. 237-239°C.

Example 23

a) A stirred mixture of 4-hydroxy-6-methoxycoumarin (15 g), 3,4-dichlorophenylhydrazine (23.8 g) and dry toluene (200 ml) was refluxed for 5 hours. A further portion of the hydrazine (12.4 g) was added and refluxing continued for a further 3 hours. The reaction mixture was cooled to ambient temperature and the solid collected by filtration digested with dichloromethane and then dried to give 1-(3,4-dichlorophenyl)-3-(2-hydroxy-5-methoxyphenyl)-2-pyrazolin-5-one, m.p. 210-211°C.

b) A stirred mixture of 1-(3,4-dichlorophenyl)-3-(2-hydroxy-5-methoxyphenyl)-2-pyrazolin-5-one (20 g) aluminium chloride (34 g), and xylene (280 ml) were heated on a steam bath for 6 hours. The xylene was decanted off and the remaining mixture poured into a mixture of ice and 1M hydrochloric acid with stirring. The mixture was stirred for an hour, stored at ambient temperature for a 18 hours, and filtered to give 1-(3,4-dichlorophenyl)-3-(2,5-dihydroxyphenyl)-2-pyrazolin-5-one.

Example 24

A stirred mixture of 4-hydroxycoumarin (14.3 g) and 4-chlorophenylhydrazine (18.9 g) in dry toluene (150 ml) was heated under reflux for 2.5 hours with removal of the water produced in the reaction. The

mixture was allowed to cool to ambient temperature, then filtered and the solid product collected to give 1-(4-chlorophenyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one, m.p. 183-185°C.

Examples 25-34

In a similar manner to that described in Example 24, a compound of formula X was prepared by reacting a compound of formula XVI (in which X is oxygen, R_9 and R_{31} are hydrogen and R_{10} is as defined) with a compound of formula XV (in which Z is -CH=, R_8, is hydrogen and R_7 and R_8 are as defined) as summarised in Table 2 below.

TABLE 2

Example	XVI	XV		Amount of Reactants			Reflux Time (hours)	mp of X (°C)	Notes
	R_{10}	R_7	R_8	XVI (g)	XV (g)	Toluene (ml)			
25	H	Cl	Cl	17.2	18.8	174	4.8	196-200	(1)
26	6-F	Cl	H	6.0	7.8	60	2.5	180-183	(2)
27	H	Br	H	11.6	20.1	100	2.2	195-198	(1)
28	H	F	H	15.0	11.7	153	4.2	170-173	(1)
29	6-Me	Cl	H	17.6	21.4	150	4.0	232-234	(1)
30	H	CF_3	H	2.0	3.0	15	4.0	174-177	(1) (3)
31	H	OCH_3	H	23.1	21.7	500	2.0	133-131	(4) (5)
32	H	CH_3	H	13.4	11.1	100	2.0	180-182	(4) (5)
33	H	H	Cl	5.0	4.9	50	2.0	146-148	(4) (5)
34	5-OH	Cl	H	10.0	10.0	200	4.5	268-271	(6)

Notes

(1) The solid collected on filtration was heated with dichloromethane, hot filtered and the solid product was deposited on cooling.

(2) Filtrate concentrated under reduced pressure until crystallisation occurred.

(3) Dichloromethane extracts evaporated to dryness.

(4) The reaction solution was allowed to cool and the solid obtained following evaporation was heated with dichloromethane.

(5) Recrystallisation from acetonitrile.

(6) The solid collected on filtration was boiled with industrial methylated spirit/water (3:1), cooled and the solid product collected by filtration.

The compounds prepared in the above Examples were as follows:-

25 1-(3,4-dichlorophenyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one

26 1-(4-chlorophenyl)-3-(5-fluoro-2-hydroxyphenyl)-2-pyrazolin-5-one

27 1-(4-bromophenyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one

28 1-(4-fluorophenyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one

29 1-(4-chlorophenyl)-3-(2-hydroxy-5-methylphenyl)-2-pyrazolin-5-one

30 3-(2-hydroxyphenyl)-1-(4-trifluoromethylphenyl)-2-pyrazolin-5-one

31 3-(2-hydroxyphenyl)-1-(4-methoxyphenyl)-2-pyrazolin-5-one

32 3-(2-hydroxyphenyl)-1-(4-methylphenyl)-2-pyrazolin-5-one

33 1-(3-chlorophenyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one

34 1-(4-chlorophenyl)-3-(2,6-dihydroxyphenyl)-2-pyrazolin-5-one

Examples 35-43

In a similar manner to that described in Example 24, a compound of formula X was prepared by reacting a compound of formula XVI (in which X is oxygen, R_9 and R_{31} are hydrogen and R_{10} is as defined) with a compound of formula XV (in which Z is -N= and R_7, R_8 and R_8, are as defined) as summarised in Table 3 below.

Table 3

Example	XVI	XV			Amount of Reactants			Reflux Time (hours)	m.p. of X (°C)	Notes
	R_{10}	R_7	R_8	$R_{8'}$	XVI (g)	XV (g)	Reflux medium (ml)			
35	H	CF_3	H	H	4.9	8.0	(1c) 60/60	16	196-198	
36	H	H	Cl	H	3.1	4.0	(1a) 90	2.5	204	
37	H	Cl	H	H	3.1	4.0	(1d) 30	5	178-179	(2) (3)
38	H	H	CF_3	H	3.1	5.0	(1c) 50/50	4.3	193-195	
39	H	H	H	Cl	5.7	7.5	(1b) 400	16	211-213	(4)
40	H	CF_3	Cl	H	2.0	4.0	(1d) 25	2	200-206	
41	H	Br	H	H	2.4	3.8	(1d) 25	2.5	188-190	(5)
42	5-OH	Cl	H	H	15.0	15.0	(1d) 150	4	218-220	(2) (6) (7)
43	6-F	CF_3	H	H	10.0	14.8	(1d) 190	2.5	191-193	(8)

Notes

(1) Reactants refluxed in
a) ethyl acetate
b) xylene
c) toluene/ethyl acetate
d) toluene

(2) Ethyl acetate (50-100% of volume of toluene) added to refluxing mixture after 20 minutes.

(3) Recrystallised from ethanol.

(4) The reaction mixture was cooled and evaporated. The solid obtained was digested with ethyl acetate and hot filtered. The filtrate was evaporated and the oil obtained purified by flash chromatography on silica using 2% methanol/dichloromethane as the mobile phase. The fractions were combined and evaporated to give a solid which was recrystallised from ethyl acetate.

(5) The crude product was boiled with ethanol and filtered twice.

(6) A further portion of the hydrazine (2.0 g) was added after 3 hours.

(7) The hot reaction mixture was decanted off, concentrated and filtered. The solid collected was suspended in diethyl ether (300 ml) and extracted with 2.5M sodium hydroxide solution. The extracts were combined, washed with diethyl ether and then acidified with concentrated hydrochloric acid. The solid product was collected by filtration, washed with water and dried.

(8) After refluxing the toluene liquors were evaporated to dryness. The residue was boiled with dichloromethane, hot filtered, and the filtrate concentrated. Cooling and scratching gave the solid product which was collected by filtration.

The compounds prepared in the above Examples were as follows:-

35 3-(2-hydroxyphenyl)-1-(5-trifluoromethyl-2-pyridyl)-2-pyrazolin-5-one

36 1-(6-chloro-2-pyridyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one

37 1-(5-chloro-2-pyridyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one

38 3-(2-hydroxyphenyl)-1-(6-trifluoromethyl-2-pyridyl)-2-pyrazolin-5-one

39 1-(4-chloro-2-pyridyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one

40 1-(6-chloro-5-trifluoromethyl-2-pyridyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one

41 1-(5-bromo-2-pyridyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one

42 1-(5-chloro-2-pyridyl)-3-(2,6-dihydroxyphenyl)-2-pyrazolin-5-one

43 3-(5-fluoro-2-hydroxyphenyl)-1-(5-trifluoromethyl-2-pyridyl)-2-pyrazolin-5-one

Example 44

A stirred mixture of 4-hydroxythiocoumarin (4.5 g) and 4-trifluoromethylphenylhydrazine (7.0 g) in dry toluene (47 ml) was heated under reflux for 4.5 hours under nitrogen, adding more of the hydrazine (1.5 g) after 2 hours, with removal of the water produced in the reaction. The mixture was allowed to cool to ambient temperature, filtered and the filtrate stored

at ambient temperature for 18 hours. The filtrate was evaporated, the solid residue dissolved in dichloromethane and the solution washed with water, dried and concentrated and the solid obtained washed with dichloromethane to give 3-(2-mercaptophenyl)-1-(4-trifluoromethylphenyl)-2-pyrazolin-5-one, m.p. 161-164°C.

Preparation of Novel Compounds of Formula II'

Example 45

A stirred mixture of 1-(4-chlorophenyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one (2.9 g) and tripropyl ortho(propoxycarbonyl)acetate (8.7 g) was heated at 145-150°C for 40 minutes. The mixture was cooled below 100°C and diluted with industrial methylated spirit. The solid produced was collected by filtration to give propyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate, m.p. 138-140°C.

Example 46

In a similar manner to Example 45, a mixture of 1-(4-chlorophenyl)-3-(2,5-dihydroxyphenyl)-2-pyrazolin-5-one (6.6 g) and trimethyl ortho(isopropoxycarbonyl)-acetate (21.9 g) was heated at 140°C for 2 hours, then cooled, filtered and the solid product washed with ether to give isopropyl 2-(4-chlorophenyl)-8-hydroxy-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate, m.p. 224-225°C.

Example 47

A stirred mixture of 1-(4-chlorophenyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one (2.9 g) and triethyl

ortho(ethoxycarbonyl)acetate (7.0 g) was heated at 130-135°C for 10 minutes, then cooled and diluted with ether. The solid produced was collected by filtration to give ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate, 159-161°C.

Examples 48-60

In a similar manner to that described in Example 47, a compound of formula II' (in which R_6, is hydrogen and R_a is $COOC_2H_5$) was prepared by reacting a compound of formula X (in which Z is -CH=, R_8' and R_9 represent hydrogen and X, R_7, R_8 and R_{10} are as defined) with triethyl ortho(ethoxycarbonyl)acetate (XI) as summarised in Table 4 below:

Table 4

Example	X	R_7	R_8	R_{10}	Amounts of Reactants: X (g)	Amounts of Reactants: XI (g)	Heating Time (mins)	mp of II' (°C)	Notes
48	O	Cl	H	5-OH	5.8	13.5	15	237-239	(1)
49	O	Cl	H	5-F	3.4	7.4	10	150-152	
50	O	Cl	H	5-CH_3	2.1	6.0	15	144-147	(1)
51	O	Cl	Cl	H	3.8	7.8	10	153-154	
52	O	Br	H	H	4.2	8.9	10	150-152	
53	O	F	H	H	1.2	3.1	10	152-154	
54	O	Cl	H	6-OH	3.4	7.9	60	173-175	(3)
55	O	CF_3	H	H	3.6	7.9	20	143-146	(1) (2)
56	O	OCH_3	H	H	4.8	7.9	15	150-151	
57	O	CH_3	H	H	0.5	1.8	15	153-154	
58	O	H	Cl	H	0.5	1.6	15	172-174	
59	O	Cl	H	6-OCH_3	3.1	9.1	15	205-206	
60	S	CF_3	H	H	1.1	2.7	10	143-144	

Notes on Table 4

(1) Heating temperature = 140-150°C.

(2) After dilution with ether and filtration the solid product was stirred with dichloromethane and filtered. The filtrate was evaporated and the solid obtained triturated with ether.

(3) After storage for 18 hours a further portion of the ortho ester (5 g) was added and the mixture heated for a further 60 minutes. The mixture was triturated with ether and the solid product collected by filtration.

The compounds prepared in the above Examples were:-

48 ethyl 2-(4-chlorophenyl)-8-hydroxy-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate;

49 ethyl 2-(4-chlorophenyl)-8-fluoro-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate;

50 ethyl 2-(4-chlorophenyl)-8-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate;

51 ethyl 2-(3,4-dichlorophenyl)-3-oxo-2,3-dihydro-[1]benzopyrano[4,3-c]pyrazole-4-acetate;

52 ethyl 2-(4-bromophenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate;

53 ethyl 2-(4-fluorophenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate;

54 ethyl 2-(4-chlorophenyl)-9-hydroxy-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate;

55 ethyl 3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate;

56 ethyl 2-(4-methoxyphenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate;

57 ethyl 2-(4-methylphenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate;

58 ethyl 2-(3-chlorophenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate;

59 ethyl 2-(4-chlorophenyl)-9-methoxy-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate;

60 ethyl 3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzothiopyrano[4,3-c]pyrazole-4-acetate

Examples 61-65

In a similar manner to that described in Example 47, a compound of formula II' (in which R_a and R_6, are hydrogen) was prepared by reacting a compound of formula X (in which X is oxygen, Z is -CH=; R_8' and R_9 represent hydrogen and R_7, R_8 and R_{10} are as defined) with triethyl orthoacetate (XI) as summarised in Table 5 below:

Table 5

Example	X			Amount of Reactants		Heating Time (mins)	m.p. of II' (°C)	Notes
	R_7	R_8	R_{10}	X (g)	XI (g)			
61	Cl	H	6-OCH_3	1.1	1.9	25	226-230	
62	Cl	H	5-OH	1.4	5.6	10	315-319	
63	Cl	Cl	5-OH	17.5	28.2	30	260(d)	
64	Br	H	5-OH	1.2	1.8 ml	15	303-305	
65	CF_3	H	5-OH	0.4	0.7 ml	15	272-274	(1)

(d) = decomposition

Notes

(1) Heating temperature = 140-150°C.

The compounds prepared in the above Examples were:-

61 2-(4-chlorophenyl)-9-methoxy-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one;

62 2-(4-chlorophenyl)-8-hydroxy-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one;

63 2-(3,4-dichlorophenyl)-8-hydroxy-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one;

64 2-(4-bromophenyl)-8-hydroxy-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one;

65 8-hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-[1]benzopyrano[4,3-c]pyrazol-3(2H)-one;

Example 66

A mixture of 2-(4-chlorophenyl)-9-methoxy-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one (0.5 g) and aluminium chloride (0.78 g) in dry xylene (4.8 ml) was placed in a preheated oil bath at 100-110°C for 35 minutes. On cooling, 2M hydrochloric acid (10 ml) and ice were added to the reaction mixture. The yellow solid obtained was collected by filtration to give 2-(4-chlorophenyl)-9-hydroxy-4-methyl[1]benzopyrano-[4,3-c]pyrazol-3(2H)-one, m.p. 213-215°C.

Example 67

A solution of 3,4-dichlorophenylhydrazine (3.2 g) in xylene (75 ml) was added to a mixture of methyl 6-methoxy-3-methyl-4-oxo-3-thiochromancarboxylate (2.0 g) and p-toluenesulphonic acid (0.4 g) in xylene

(50 ml). The mixture was boiled under reflux for 22 hours, under nitrogen, with removal of the water formed in the reaction. The mixture was cooled and evaporated under reduced pressure. The residue was separated twice by flash chromatography on silica using firstly dichloromethane as the mobile phase and then dichloromethane/petroleum ether (b.p. 40-60°C, 1:1). The oil obtained was crystallised from propan-2-ol to give 2-(3,4-dichlorophenyl)-8-methoxy-3a-methyl-3a,4-dihydro[1]benzothiopyrano[4,3-c]-pyrazol-3(2H)-one, m.p. 73-76°C.

Examples 68-71

In a similar method to that described in Example 67, a compound of formula I' (in which X is sulphur, Z is -CH=, R_9 is hydrogen and R_{10}, is 8-methoxy) was prepared by reacting a compound of formula XIV (preparative example of starting compound provided) with a compound of formula XV (in which R_8, represents hydrogen and R_7 and R_8 are as defined), as summarised in Table 6 below. In each case 0.4 g p-toluenesulphonic acid was used in the reaction.

Table 6

Ex	Ex. of Starting Compound XIV	XV R_7	XV R_8	Amounts of Reactants: XIV (g)	XV (g)	Xylene (ml)	Reflux Time (hours)	m.p. of I' (°C)	Notes
68	2	CF_3	H	5.5	7.3	200	16	147-148	(1a) (2)
69	2	Cl	H	5.0	13.5	200	16	147-149	(1a) (2)
70	2	F	H	5.0	6.1	200	16	174-176	(1b) (2)
71	3	CF_3	H	5.3	5.0	200	18	190-191	(1a) (3) (4a)
71a	3	Cl	Cl	16.2	18.5	400	2	192-193	(4b) (1a)

Notes

(1) Single flash chromatographic purification process using as the mobile phase:-

a) dichloromethane

b) dichloromethane/methanol (99.5:0.5)

(2) Recrystallised from isopropyl alcohol.

(3) 0.2 g p-toluenesulphonic acid used.

(4) The reaction mixture was filtered and the filtrate was:-

a) concentrated to give a solid which was crystallised from methanol; or

b) evaporated to give a solid which was crystallised from methanol followed by flash chromatography.

The compounds prepared in the above Examples were as follows:-

68 8-methoxy-3a-methyl-2-(4-trifluoromethylphenyl)-3a,4-dihydro[1]benzothiopyrano[4,3-c]pyrazol-3-(2H)-one

69 2-(4-chlorophenyl)-8-methoxy-3a-methyl-3a,4-dihydro[1]benzothiopyrano[4,3-c]pyrazol-3(2H)-one

70 2-(4-fluorophenyl)-8-methoxy-3a-methyl-3a,4-dihydro[1]benzothiopyrano[4',3-c]pyrazol-3(2H)-one

71 8-methoxy-4-methyl-2-(4-trifluoromethylphenyl)-[1]benzothiopyrano[4,3-c]pyrazol-3(2H)-one

Example 72

Boron tribromide (21.4 ml), (1M solution in

dichloromethane) was added dropwise to a mixture of 8-methoxy-3a-methyl-2-(4-trifluoromethylphenyl)-3a,4-dihydro[1]benzothiopyrano[4,3-c]pyrazol-3(2H)-one (4.2 g) in dry dichloromethane (80 ml) at -70°C with stirring under nitrogen. The mixture was stirred at ambient temperature for 1 hour. The reaction mixture was poured onto methanol (800 ml) followed by evaporation under reduced pressure. The oil obtained was dissolved in ethyl acetate, washed with water and then aqueous sodium bicarbonate solution (10%), and the ethyl acetate layer dried and evaporated. The solid was recrystallised from ethyl acetate/petroleum ether (b.p. 40-60°C) to give 8-hydroxy-3a-methyl-2-(4-trifluoromethylphenyl)-3a,4-dihydro[1]benzothiopyrano-[4,3-c]pyrazol-3-(2H)-one, m.p. 211-213°C.

Examples 73-76

In a similar manner to that described in Example 72, a compound of formula I' (in which X is sulphur, Z is -CH=, R_9 is hydrogen and R_{10}' is 8-hydroxy) was prepared from a compound of formula I' (in which R_{10}' is 8-methoxy- preparative example of starting compound provided) as summarised in Table 7 below. In Example 76a a further portion of boron tribromide was added to the reaction mixture cooled to -70°C, as shown in the Table.

Table 7

Example	Ex. of Starting Compound I'	Amounts of Reactants: I' (g)	Amounts of Reactants: BBr_3 (ml)	Amounts of Reactants: Dichloromethane (ml)	Reaction Time (hours)	m.p. of Product I' (°C)	Notes
73	67	1.0	2.5	15	26	185-188	(1)
74	69	2.2	12.0	40	1	214-216	
75	70	4.0	23.4	60	16	208-212	
76	71	1.0	5.2	15	18	275-277	(2) (3)
76a	71a	1.0	2.6	15	16	312-314	(3)
			1.3		24		

Notes

(1) A further portion of BBr_3 (5.5 ml) was added after 18 hours. The residue obtained after treatment with methanol and recrystallisation from ethyl acetate and sodium bicarbonate was separated by flash chromatography on silica using dichloromethane as the mobile phase to give a solid which was recrystallised from ether/petroleum ether (b.p. 40-60°C).

(2) A further portion of BBr_3 (5.2 ml) was added after 2 hours.

(3) The solid produced on pouring the reaction mixture on to methanol was filtered and dried to give the product.

The compounds prepared in the above Examples were as follows:-

73 2-(3,4-dichlorophenyl)-8-hydroxy-3a-methyl-3a,4-dihydro[1]benzothiopyrano[4,3-c]pyrazol-3(2H)-one;

74 2-(4-chlorophenyl)-8-hydroxy-3a-methyl-3a,4-dihydro[1]benzothiopyrano[4,3-c]pyrazol-3-(2H)-one;

75 2-(4-fluorophenyl)-8-hydroxy-3a-methyl-3a,4-dihydro[1]benzothiopyrano[4,3-c]pyrazol-3-(2H)-one;

76 8-hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-[1]benzothiopyrano[4,3-c]pyrazol-3(2H)-one;

Preparation of Novel Compounds of Formula I

Examples 77-90

In a similar manner to that described in Example 47, a compound of formula I was prepared by reacting a compound of formula X (in which X is oxygen, Z is -N=, R_9 is hydrogen, and R_7, R_8, R_8, and R_{10} are as defined) with triethyl orthoacetate (XI) as summarised in Table 8 below:

Table 8

Example	X				Amounts of Reactants		Heating Time (mins)	m.p. of I (°C)	Notes
	R_7	R_8	$R_{8'}$	R_{10}	X (g)	XI (ml)			
77	CF_3	H	H	H	1.7	4.8	15	225-227	(1)
78	Cl	H	H	H	2.0	3.1	15	242	(1) (2)
79	H	Cl	H	H	1.3	4.4	15	231	(1)
80	H	CF_3	H	H	2.0	10.3	150	176-184	(1)
81	H	H	Cl	H	1.4	15.4	60	181-186	(1)
82	CF_3	Cl	H	H	1.0	3.0	10	283-286	
83	Br	H	H	H	2.0	6.4	60	238-239	
84	Cl	H	H	6-OH	4.0	10.0	30	254-255	(3)
85	CF_3	H	H	5-F	0.1	0.6	10	265-269	
86	Cl	H	H	5-F	2.0	7.2	15	262-263	(4)

Notes

(1) Heating temperature = 140-150°C

(2) Recrystallised from ethanol/dichloromethane

(3) The crude product was purified by flash chromatorgraphy on silica using a 4% solution of methanol in dichloromethane. The extracts were combined, triturated with dichloromethane/petroleum ether (b.p. 40-60°C) and then acetone and then dried under reduced pressure to give the product.

(4) A further portion of the orthoacetate (7.2 ml) was added after 5 minutes. The solid produced from the reaction mixture was triturated with industrial methylated spirit.

Example 87

In a similar manner to that described in Example 47, a stirred mixture of 1-(5-chloro-2-pyridyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one (1.4 g) and trimethyl ortho(methylthio)acetate (2.5 ml) was heated at 140-145°C for 10 minutes, then cooled and triturated with industrial methylated spirit, to give 2-(5-chloro-2-pyridyl)-4-methylthiomethyl[1]benzopyrano-[4,3-c]pyrazol-3(2H)-one, m.p. 217-219°C.

Example 88

In a similar manner to that described in Example 47, a stirred mixture of 1-(5-chloro-2-pyridyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one (3.0 g) and triethyl ortho(ethoxycarbonyl)acetate (7.3 g) was stirred at 140-145°C for 45 minutes, adding further portions of the ortho ester (2 x 3.7 g), after 15 and 30 minutes.

The reaction mixture was cooled and triturated with ether. The solid obtained was dissolved in methylene chloride and passed down a Florisil® column eluting with methylene chloride . The eluant was evaporated and the residue triturated with ether to give ethyl 2-(5-chloro-2-pyridyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate, m.p. 152-154°C.

Example 89

Acetyl chloride (0.5 ml) was added dropwise to a stirred mixture of 2-(5-chloro-2-pyridyl)-9-hydroxy-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one (2.0 g), dry tetrahydrofuran (30 ml) and triethylamine (1.0 ml) at 0°C. The mixture was allowed to warm to ambient temperature and then stirred for 2,5 hours. A solid was collected on filtration which was washed with water and triturated with hot ethanol then dried to give 2-(5-chloro-2-pyridyl)-4-methyl-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazol-9-yl acetate, m.p. 252-255°C.

Example 90

A stirred mixture of ethyl 2-(5-chloro-2-pyridyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (1.4 g) and cyclobutylmethanol (3.5 ml) was heated at 150°C for 1 hour. The reaction mixture was allowed to cool to ambient temperature, triturated with ether and the solid product collected by filtration and washed with ether to give cyclobutylmethyl 2-(5-chloro-2-pyridyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate, m.p. 157-160°C.

Example 91

A mixture of propyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate

(1.9 g) and 2-piperidinoethanol (6.4 ml) was stirred at 150°C for 1 hour. The reaction mixture was cooled to room temperature and poured on to water (30 ml). This mixture was extracted with dichloromethane and the combined organic extracts were washed well with water, dried and evaporated. The residual oil was dissolved in absolute ethanol and treated with ethanolic hydrogen chloride. The solid formed on cooling and scratching was collected by filtration and dried giving 2-piperidinoethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro-[1]benzopyrano[4,3-c]pyrazole-4-acetate hydrochloride, m.p. 193-197°C (with decomposition).

Examples 92-100

In a similar manner to that described in Example 91, a compound of formula I was prepared by reacting a compound of formula II' (the Example for the preparation of the starting ester is provided) with the appropriate alcohol as summarised in Table 9 below.

Table 9

Example	Ex. of Starting Ester II'	Alcohol	Amount of Reactants: Ester II' (g)	Amount of Reactants: Alcohol (ml)	Time (mins)	m.p. of I (°C)	Notes
92	45	(4-methyl-1-piperazinyl)-$CH_2CH_2CH_2OH$	1.7	6.8 g	30	200 (d)	
93	47	(morpholino) CH_2CH_2OH	1.9	6.0	15	213-215	
94	51	(morpholino) CH_2CH_2OH	2.0	6.0	10	145-147	(1)
95	48	(morpholino) CH_2CH_2OH	1.8	6.9	15	75-79	(2)
96	47	(morpholino) $CH_2CH_2CH_2OH$	1.7	6.4	25	185-190	(3)
97	52	(morpholino) CH_2CH_2OH	1.5	4.2	15	198-203	
98	53	(morpholino) CH_2CH_2OH	2.2	7.5	25	213-216	
99	49	(morpholino) CH_2CH_2OH	2.0	6.0	10	204-208	
100	59	(morpholino) CH_2CH_2OH	1.5	4.4	25	187-190	

(d) = decomposition

Notes

(1) Product converted into its free-base using triethylamine and purified by flash chromatography on silica using dichloromethane/methanol (9:1) as the mobile phase.

(2) After heating at 150°C for 15 minutes, the reaction mixture was diluted with dichloromethane (100 ml) and washed with water. The solid product which separated was collected by filtration.

(3) Product softens at 55°C.

Example 101

A mixture of ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (3.0 g) and 4-methoxybenzyl alcohol (9.6 ml) was stirred at 150°C for 50 minutes. The reaction mixture was cooled to ambient temperature, diluted with ether and the product collected by filtration to give 4-methoxybenzyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro-[1]benzopyrano-[4,3-c]pyrazole-4-acetate, m.p. 152-155°C.

Examples 102-134

In a similar manner to that described in Example 101, a compound of formula I was prepared by reacting ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro-[1]-benzopyrano[4,3-c]pyrazole-4-acetate (II') with the appropriate alcohol, as summarized in Table 10 below.

Table 10

Ex	Alcohol	Amount of Reactants: Ester II' (g)	Amount of Reactants: Alcohol (ml)	Time (mins)	m.p. of I (°C)	Notes
102	$PhCH_2OH$	3.0	8.1	70	165-166	
103	$Ph(CH_2)_2OH$	2.0	6.4g	80	153-156	
104	(cyclopentyl)OH	2.0	4.8	80	169-172	
105	$CH_3OCH_2CH_2OH$	2.0	40	60	125-126	(1a)
106	(2-thienyl)CH_2CH_2OH	2.0	9.0g	360	122-123	(1a) (2a) (3a)
107	(cyclobutyl)CH_2OH	2.0	5.0	120	138-139	(4a)
108	(2-pyridyl)CH_2CH_2OH	2.0	6.0	15	124-127	(5)
109	(cyclobutyl)OH	2.1	4.0g	105	148-150	(4a)
110	$CH_3O(CH_2)_2O(CH_2)_2OH$	2.0	6.2	105	104-106	(4a)
111	(2-tetrahydrofuryl)CH_2OH	2.0	5.0	150	133-136	(1c) (4a)
112	(4-tetrahydropyranyl)OH	2.0	7.2	300	189-190	(4a)
113	(4-methyl-5-thiazolyl)CH_2CH_2OH	2.0	6.2	270	134-136	(1c) (4a)

Table 10 cont'd

Ex	Alcohol	Amount of Reactants: Ester (g) II'	Amount of Reactants: Alcohol (ml)	Time (mins)	m.p. of I (°C)	Notes
114	(3-methoxybenzyl)OH	2.0	6.4	80	127-130	(3b)
115	(4-methylbenzyl)OH	2.2	7.0g	90	182-185	(3b) (6a)
116	(4-methoxyphenethyl)OH	1.0	3.95g	90	123-126	(3b) (6a)
117	(4-chlorophenyl)CH_2CH_2OH	1.0	3.5	60	94-97	(1a)
118	(2-chlorophenyl)CH_2OH	1.0	3.7g	250	124-127	(6b)
119	(acetyl)CH_2CH_2OH	2.0	4.6g	35	130-132	(4a)
120	(2-chlorophenyl)CH_2CH_2OH	1.4	4.0g	120	132-135	(6a)
121	(3-methylphenyl)CH_2CH_2OH	1.4	5.0	120	126-128	(6a)
122	(cyclohexyl)OH	2.0	5.0	60	176-178	(4a)
123	(3-chlorophenyl)CH_2OH	1.0	3.1	150	110-113	(6b) (8a)
124	1,3-propanediol	1.0	2.0	60	138-140	(3d) (3c) (4a)

Table 10 Cont'd

Ex	Alcohol	Amount of Reactants: Ester II' (g)	Amount of Reactants: Alcohol (ml)	Time (mins)	m.p. of I (°C)	Notes
125	(phenoxy)CH_2CH_2OH	1.4	4.4	60	122	(2b) (1e)
126	(4-dimethylaminophenyl)CH_2CH_2OH	1.2	2.5	15	192-194	(6a)
127	(acetylamino)CH_2CH_2OH	1.5	3.6	40	183-186	(1d) (4c)
128	(3-methylphenyl)CH_2OH	1.1	3.5g	180	149-153	(6a)
129	(2-methylphenyl)CH_2OH	1.1	3.5g	150	148-150	(6a)
130	(4-chlorophenyl)CH_2OH	1.0	3.7g	210	171-173	(3b) (7b)
131	(2-methoxyphenyl)CH_2OH	1.0	3.6g	180	165-167	(3b) (6a)
132	(3-pyridyl)$CH_2CH_2CH_2OH$	1.5	5.1	15	117-119	(1b) (1b) (12)
133	(benzyl)$CH(CH_3)OH$	2.0	3.7	600	110-113	(2a) (3c) (4b)
			2.0	300		
134	(cyclopropyl)CH_2OH	2.0	4.0	90	162-165	

Notes

(1) The cooled reaction mixture:-
a) yielded a solid which was collected by filtration;
b) yielded a solid which was triturated with toluene and ether;
c) was dissolved in dichloromethane, washed with water, dried and evaporated;
d) was dissolved in dichloromethane, washed with water, dried and evaporated and the resulting gum triturated with ether;
e) was poured into water, the solid collected by filtration.

(2) The product was recrystallised from:-
a) acetonitrile;
b) ethyl acetate.

(3) The reaction mixture was heated at:-
a) 120°C;
b) 150-160°C;
c) 180°C;
d) 214°C.

(4) The crude product was purified by flash chromotography on silica using, as a mobile phase:-
a) toluene/acetic acid (9:1);
b) toluene;
c) ethyl acetate/acetic acid (9:1).
The fractions obtained were evaporated and triturated with ether to give the product.

(5) The cooled reaction mixture was dissolved in dichloromethane and washed with water. After drying and concentration, the mixture was purified on a

Florisil® column using dichloromethane containing increasing amounts of acetone (from 1 to 10%) as the mobile phase. The material obtained was triturated with ether to give the product.

(6) The reaction mixture was cooled to about 90°C then diluted with:-

a) industrial methylated spirit;

b) absolute ethanol.

The product was collected by filtration.

Examples 135-141

In a similar manner to that described in Example 101, a compound of formula I was prepared by reacting a compound of formula II' (the Example for the preparation of the starting ester is provided) with the appropriate alcohol as summarized in Table 11 below.

Table 11

Example	Ex. of Starting Ester II'	Alcohol	Amount of Reactants: Ester II' (g)	Amount of Reactants: Alcohol (ml)	Time (mins)	m.p. of I (°C)	Notes
135	55	(cyclobutane)CH_2OH	1.5	3.5	90	128-129	
136	50	(cyclobutane)CH_2OH	1.2	2.9	90	173-174	
137	56	(cyclobutane)CH_2OH	1.5	3.4	150	128-131	
138	57	(cyclobutane)CH_2OH	1.0	2.4g	280	99-101	
139	58	(cyclobutane)CH_2OH	2.0	4.9	300	144-146	
140	54	(cyclobutane)CH_2OH	3.7	7.9g	26	180-182	(1)
141	48	(cyclobutane)CH_2OH	2.0	4.8	60	166-168	

Notes

(1) Cycle included 26 hours refluxing and 140 hours storage at ambient temperature. A further portion of the alcohol (2 g) was added after 13 hours refluxing.

Examples 142 and 143

A mixture of ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (2.0 g), 1,2-ethanediol acetate (2.0 ml, ca 1:1 mixture of the mono and diacetate), N-methylmorpholine (0.6 ml) and dry xylene (20 ml) was heated under reflux for 6 hours. The mixture was evaporated under reduced pressure and the residue separated by flash chromatography on silica using toluene/acetic acid (9:1) as the mobile phase. This gave 2-acetoxyethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro-[1]benzopyrano [4,3-c]pyrazole-4-acetate (Example 142 m.p. 136-139°C, and 2-hydroxyethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (Example 143), m.p. 161-162°C.

Example 144

A mixture of ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (2.0 g), 4-(2-hydroxyethyl)thiomorpholine (1 g), dry xylene (20 ml) and N-methylmorpholine (0.6 ml) containing 4A molecular sieves was stirred and heated at 150°C for 3 hours. More 4-(2-hydroxyethyl)thiomorpholine (1.0 g) was added and heating was continued for 1 hour. The reaction mixture was cooled to ambient temperature and diluted with ethyl acetate. After decanting from the molecular sieves, the solution was washed with water, dried and evaporated under reduced pressure. The residual gum was dissolved in ethanol, treated with

ethanolic hydrogen chloride and then cooled to 0°C. The solid formed was collected by filtration and dried to give 2-thiomorpholinoethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate hydrochloride, m.p. 223-226°C.

Example 145

A mixture of ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (2.00 g), 2-methylthioethanol (0.5 ml), N-methyl-morpholine (0.6 ml) and dry xylene (40 ml) was stirred at 170°C for 5 hours. The mixture was evaporated under reduced pressure and the residue recrystallised twice from acetonitrile to give 2-methylthioethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro-[1]benzopyrano[4,3-c] pyrazole-4-acetate, m.p. 113-114°C.

Example 146

A mixture of ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (2.0 g), 4,4,4-trifluorobutanol (1.3 g), N-methyl-morpholine (0.6 ml) and dry xylene (40 ml) was stirred and boiled under reflux or 5 hours. More xylene (10 ml) and more 4,4,4-trifluorobutanol (1.5 g) were added. The mixture was boiled under reflux for a further 2 hours and then evaporated under reduced pressure. The solid residue was recrystallised twice from acetonitrile to give 4,4,4-trifluorobutyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate, m.p. 114-115°C.

Example 147

A mixture of ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate

(2.0 g), 2-cyanoethanol (0.4 ml), N-methylmorpholine (0.6 ml) and molecular sieves (20 pieces) was stirred in dry xylene (40 ml) at 170°C for 5 hours. More 2-cyanoethanol (0.4 ml) was added and the mixture was stirred at 170°C for 18 hours. The mixture was evaporated under reduced pressure and the residual oil purified on a short Florisil^{R} column using dichloromethane as the mobile phase. The material obtained was separated using flash chromatography on a silica column using toluene/acetic acid (9:1) as the mobile phase. The material obtained after removal of the solvent was triturated with petroleum ether (b.p. 60-80°C) and filtered to give 2-cyanoethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate, m.p. 120-122°C.

Example 148

In a similar manner to Example 145, a mixture of ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (2.0 g), ethyl 3-hydroxypropionate (1.2 ml), N-methylmorpholine (0.6 ml) and dry xylene (40 ml) was heated at 170°C for six hours to give, after flash chromatography on silica using toluene/acetic acid (9:1) as the mobile phase, 2-ethoxycarbonylethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate, m.p. 126-129°C.

Example 149

In a similar manner to Example 145, a mixture of ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (1.1 g), 2-phenyl-1-propanol (0.4 ml) and N-methylmorpholine (0.3 g) in dry xylene (3 ml) was stirred and boiled under reflux for 15 hours, adding more 2-phenyl-1-propanol (0.2 ml) and

N-methylmorpholine (0.2 ml) after 14 hours. The reaction mixture was cooled, the solid collected by filtration and recrystallised from acetonitrile to give ß-methylphenethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro-[1]benzopyano[4,3-c]pyrazole-4-acetate, m.p. 86-90°C.

Example 150

A mixture of ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (2.0 g), cyclohexylethanol (0.7 ml), N-methylmorpholine (0.6 ml) and xylene (40 ml) was heated under reflux for 6 hours. A further portion of cyclohexylethanol (0.7 ml) was added and the mixture heated under reflux for a further 3 hours. The mixture was evaporated under reduced pressure and the residue recrystallised twice from acetonitrile to give 2-cyclohexylethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]-pyrazole-4-acetate, m.p. 149-151°C.

Example 151

A solution of ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (1.0 g), 1-methyl-2-morpholinoethanol (0.8 ml) and dry toluene (10 ml) was stirred and heated under continuous distillation for 9 hours with addition of fresh toluene to maintain the initial volume. More 1-methyl-2-morpholinoethanol (0.8 ml) was added and heating/-distilling continued for 7 hours. More 1-methyl-2-morpholinoethanol (0.8 ml) was added and the mixture heated for a further 5 hours. The reaction mixture was cooled to 0°C and the solid obtained collected by filtration, washed with ether and dried to give 1-methyl-2-morpholinoethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate, m.p. 176-179°C.

Example 152

In a similar manner to Example 151, a mixture of ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (1.0 g), (1-methyl-2-piperidyl)methanol (0.7 ml) and toluene (15 ml) gave, after flash chromatography, 1-methyl-2-piperidylmethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano-[4,3-c]pyrazole-4-acetate, m.p. 159-163°C.

Example 153

A stirred suspension of 2-morpholinoethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate hydrochloride (1.5 g) in absolute ethanol (50 ml) at 0-5°C was treated portionwise with sodium borohydride (0.6 g). The reaction mixture was stirred for 4 hours at this temperature with 3 further portions of sodium borohydride (0.28 g, 0.28 g, 0.14 g) added after 1 hour, 3 hours and 3.5 hours respectively. The reaction mixture was poured onto water, cooled to 0-5°C and neutralised with glacial acetic acid. The aqueous layer was extracted with dichloromethane. The extracts were washed, dried and evaporated to give 2-morpholino-ethyl 2-(4-chlorophenyl)-3-oxo-1,2,3,4-tetrahydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate, m.p. 125-128°C.

Example 154

Acetyl chloride (2.3 ml) and triethylamine (1.1 ml) were added to a solution of 3-hydroxypropyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano-[4,3-c]-pyrazole-4-acetate in dichloromethane (75 ml) (Example 124) at 0°C. The reation mixture was stirred at room temperature for 18 hours, then washed, dried, filtered and the filtrate evaporated. The residual

mixture was passed down a Florisil® column using dichloromethane as the mobile phase. The required fractions were combined and evaporated. The crude product was purified by flash chromatography on silica using ethyl acetate as the mobile phase. The product was recrystallised from ethyl acetate to give 3-acetoxypropyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro-[1]benzopyrano[4,3-c]pyrazole-4-acetate, m.p. 129-131°C.

Example 155

A stirred mixture of ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (1.9 g) (Example 47), N-methylaniline (0.5 g) and xylene (15 ml) was heated under reflux for 22 hours. More N-methylaniline (0.3 g) was added and the mixture heated under reflux for a further 5 hours. The mixture was cooled and scratched. The solid formed was collected by filtration and dried to give 2-(4-chlorophenyl)-N-methyl-3-oxo-2,3-dihydro[1]benzopyrano-[4,3-c]pyrazole-4-acetanilide, m.p. 200-202°C.

Examples 156-170

In a similar manner to that described in Example 155, a compound of formula I was prepared by reacting a compound of formula II' (the Example for the preparation of the starting ester is provided) with the appropriate amine as summarised in Table 12 below.

Table 12

Ex	Example of starting ester II'	Amine	Amount of Reactants: Ester (g)	Amine (g)	Xylene (ml)	Time (hours)	m.p. I	Notes
156	47	(benzyl)$NHCH_3$	3.8	1.2	30	5	168-171	(6)
157	47	(2-morpholinoethyl)-$NHCH_3$	1.9	0.7	15	24	180-183	
158	47	(3-pyridyl)CH_2NHCH_3	3.0	1.0	50	4	175-178	(2)
159	47	(phenyl)NHC_2H_5	2.0	1.3	30	4.5		
				1.3		5.5		
				1.3		7.0	201-204	(1)
160	52	(benzyl)$NHCH_3$	0.8	0.2	3	5	172-173	
161	51	(benzyl)$NHCH_3$	1.5	0.5ml	6	5	138-142	
162	49	(benzyl)$NHCH_3$	1.7	0.5ml	7	7	189-192	
163	47	(phenethyl)$NHCH_3$	1.2	0.4ml	15	12	149-151	
164	47	(2-cyanoethyl)$NHCH_3$	1.2	0.3ml	15	5	156-160	
165	47	morpholine	3.0	1.4ml	50	4	246-247	(3)

Table 12 cont'd

Ex	Example of starting ester II'	Amine	Amount of Reactants: Ester (g)	Amine (g)	Xylene (ml)	Time (hours)	m.p.	Notes
166	47	(4-chlorophenyl)$NHCH_3$	1.9	0.8	15	20	152-154	(4)
				0.35		6		
167	53	(benzyl)$NHCH_3$	1.5	0.5	7	5	164-166	
168	47	CH_3NHCH_2(1,3-dioxolan-2-yl	2.0	1.2	30	2.0	176-178	(5)
169	47	(4-methoxycarbonylphenyl)- $NHCH_3$	1.2	0.5	9	20	208-210	
				0.5		72		

Notes

(1) The solid was recrystallised from acetonitrile.

(2) The reaction mixture was evaporated under reduced pressure and the residue recrystallised from dichloromethane/industrial methylated spirit (33:1).

(3) The solid obtained was collected by filtration then dissolved in dichloromethane, filtered and industrial methylated spirit added to the filtrate. The solution was concentrated under reduced pressure cooled and the solid collected by filtration.

(4) The solid was recrystallised from acetone.

(5) The reaction mixture was evaporated and the residue was recrystallised from acetonitrile.

(6) Softened at 158°C.

Example 170

a) A mixture of propyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (1.9 g) (Example 45) and 1-piperazineethanol (5.9 ml) was stirred and heated at 150°C for 1.5 hours. The mixture was cooled to ambient temperature, diluted with water and extracted with dichloromethane. The combined organic extracts were washed with water, dried and evaporated. The residue was dissolved in ethanol and treated with ethanolic hydrogen chloride. The solid formed on cooling and scratching was collected by filtration to give 2-(4-chlorophenyl)-N,N-[3-(2-hydroxyethyl)-3-azapentamethylene]-3-oxo-2,3-dihydro-[1]benzopyrano[4,3-c]pyrazole-4-acetamide hydrochloride, 200-205°C (with decomposition).

b) A solution of 2-(4-chlorophenyl)-N,N-[3-(2-hydroxyethyl)-3-azapentamethylene]-3-oxo-2,3-dihydro [1]benzopyrano[4,3-c]pyrazole-4-acetamide hydrochloride (0.7 g) in dichloromethane (28 ml) was cooled to 0°C with stirring and treated with triethylamine (0.42 ml) followed by acetyl chloride (0.14 ml). The mixture was stirred in an ice-bath for 2 hours. More acetyl chloride (0.07 ml) was added and the mixture stirred at 0°C for a further 30 minutes then left at 0°C overnight. The mixture was washed with water, then dried and evaporated under reduced pressure. The solid obtained was triturated with ether and the solid formed collected by filtration and dried to give 2-{4-[2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetyl]piperazin-1-yl}ethyl acetate, m.p. 162-166°C.

Example 171

A stirred mixture of 2-(4-chlorophenyl)-N,N-[3-(2-hydroxyethyl)-3-azapentamethylene]-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetamide hydrochloride (0.8 g) (Example 170a) and dichloromethane (45 ml) was treated with triethylamine (0.5 ml) followed by propionyl chloride (0.3 ml) at 0°C. The reaction mixture was stirred at this temperature for 3.5 hours. The mixture was washed with water then dried and evaporated under reduced pressure. The solid obtained was triturated with ether and the solid formed collected by filtration and dried to give 2-{4-[2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetyl]piperazine-1-yl}ethyl propionate, m.p. 173-175°C.

Example 172

A stirred a mixture of ethyl 3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzothiopyrano-[4,3-c]pyrazol-4-acetate (0.9 g) (Example 60), morpholine (0.4 ml) and dry xylene (3.5 ml) was heated under reflux for 2.3 hours. The reaction mixture was allowed to cool to ambient temperature and the solid collected by filtration was washed with xylene and ether and then dissolved in dichloromethane. The solution was washed with water, dried, evaporated and triturated with ether with scratching. The solid product was collected by filtration to give N,N-(3-oxapentamethylene)-3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzothio-pyrano[4,3-c]pyrazole-4-acetamide, m.p. 210-212°C.

Example 173

A stirred mixture of ethyl 3-oxo-2-(4-tri-

fluoromethylphenyl)-2,3-dihydro[1]benzothiopyrano-[4,3-c]pyrazol-4-acetate (0.6 g), (Example 60) N-ethylaniline (0.4 ml) and dry xylene (2.4 ml) was heated under reflux for 4 hours. A further portion of N-ethylaniline (0.1 ml) was added and the reaction mixture refluxed for a further 2 hours. The reaction mixture was stored at ambient temperature for 72 hours and a further portion N-ethylaniline (0.2 ml) added with refluxing for a further 3 hours. The solid product was collected by filtration, washed with xylene and ether to give N-ethyl-3-oxo-N-phenyl-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzothiopyrano-[4,3-c]pyrazol-4-acetamide, m.p. 179-181°C.

Example 174

A mixture of 1-(4-chlorophenyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one (17.0 g) and methyl 4-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-oxobutyrate (30.0 g) (Example 4) was stirred and heated under reflux in xylene (200 ml) under nitrogen for 6 hours. The mixture was cooled to ambient temperature, the solvent evaporated and the resulting solid recrystallised from propan-2-ol to give methyl 5-[2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazol-4-yl]-4-oxopentanoate, m.p. 142-143°C.

Examples 175-186

In a similar manner to that described in Example 174 a compound of formula I was prepared by reacting a compound of formula X (in which X is oxygen, Z is -CH= and R_8' and R_9 are hydrogen, and R_7, R_8 and R_{10} are as defined) with a compound of formula XIIb (the Example for the preparation of the starting compound XIIb is provided) as summarised in Table 13 below:

Table 13

Example	Ex. of Starting cpd XIIb	X			Amounts of Reactants			Reaction Time	m.p. of I	Notes
		R_7	R_8	R_{10}	X (g)	XIIb (g)	Xylene (ml)	(hours)	(°C)	
175	5	Cl	H	H	5.7	11.5	120	6	146-147	(1)
176	6	Cl	H	H	5.0	12.1	100	6	160-162	(1)
177	7	Cl	H	H	5.7	12.2	120	6	176-177	(2)
178	8	Cl	H	H	6.8	12.9	120	6	151-153	(2)
179	9	Cl	H	H	4.0	9.7	50	6	152-154	(3)
180	10	Cl	H	H	2.5	7.0	50	6	188-189	(4)
181	11	Cl	H	H	3.0	6.3	50	3		
						1.0		4	146-148	(5)
182	12	Cl	H	H	2.0	4.1	30	1	159-161	(6)
183	13	Cl	H	H	2.5	5.3	50	2	198-199	(7)
184	14	Cl	H	H	12.0	23.8	200	1.5	115-118	(8)
185	6	Cl	Cl	H	3.0	6.8	55	3.5	192-193	(9)
186	15	Cl	H	H	5.0	9.1	120	6	139-141	(1)

Notes

(1) After removal of the solvent, the resultant oil was taken up in propan-2-ol. The solution was treated with charcoal, hot filtered and the filtrate concentrated. The resulting solid was collected by filtration, washed with ether and recrystallised from propan-2-ol.

(2) Recrystallised from industrial methylated spirit.

(3) Recrystallised from methanol.

(4) On cooling the reaction mixture the solid product was filtered off.

(5) Solid triturated with ether, filtered, washed and dried to give product.

(6) On evaporation of the reaction mixture and scratching a solid was produced which was triturated with hot industrial methylated spirit, washed and dried to give the product.

(7) Solid product obtained on filtration after cooling the reaction mixture to room temperature.

(8) Reaction mixture allowed to cool to ambient temperature and kept at this temperature for 18 hours. After decanting off the solution, cooling and scratching gave the solid product.

(9) Allowed to cool to ambient temperature over 18 hours. The solid collected by filtration was recrystallised from ethyl acetate with hot filtration.

Example 187

A stirred mixture of 2-(4-chlorophenyl)-9-hydroxy-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one (2.0 g) (Example 66), triethylamine (1.4 g) and dichloromethane (20 ml) was cooled in an ice bath while methyl malonyl chloride (1.5 ml) was added. More dichloromethane (20 ml) was added and the mixture allowed to warm up to ambient temperature over 18 hours. The mixture was filtered and the residue washed with dichloromethane and then water. This residue was recrystallised from acetonitrile to give 2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihvdro[1]benzopyrano[4,3-c]pyrazol-9-yl methyl malonate, m.p. 204-206°C.

Examples 188-206

In a similar manner to that described in Example 187, a compound of formula I was prepared by reacting 2-(4-chlorophenyl)-8-hydroxy-4-methyl[1]benzopyrano-[4,3-c]pyrazol-3(2H)-one (Example 62) with the appropriate acyl chloride ($R_{17}COCl$) as summarised in Table 14 below.

Table 14

Example	R_{17}	Amounts of Reactants: II' (g)	$R_{17}COCl$ (ml)	Et_3N (ml)	m.p. of I (°C)	Notes
188	$C_2H_5OOCCH_2$	2.0	2.0	2.0	114-116	(1)
189	CH_3OCH_2	2.0	1.1	1.7	168-170	(1)
190	cyclopropane	1.5	0.9	1.5	215-219	(3) (1)
191	adamantyl	1.5	2.0	1.5	252-255	(3) (1)
192	phenethyl	1.5	1.5	1.5	177-178	(2) (3)
193	benzyl	1.5	1.5	1.5	195-198	(2) (3)
194	2-methoxyphenyl	2.0	1.8	3.4	205-208	
195	2-furyl	2.0	1.1	3.4	217-218	
196	2-thienyl	2.0	1.2	3.4	238-242	
197	cyclobutane	2.0	1.6	1.6	208-210	(2) (3)
198	2-methylphenyl	2.0	1.4	3.4	221-222	
199	4-chlorophenyl	2.0	1.6	2.0	244-247	
200	$CH_3CH=CH$	2.0	1.2	2.0	159-162	(1) (3)
201	4-methoxyphenyl	1.4	1.5	1.2	200-202	(5) (6)
202	4-methylphenyl	1.4	1.2	1.2	216-218	(3) (6)

Table 14 Cont'd

Example	R_{17}	Amounts of Reactants: II' (g)	$R_{17}COCl$ (ml)	Et_3N (ml)	m.p. of I (°C)	Notes
203	cyclopentane	1.5	1.3g	1.5	208-209	(2) (3)
204	cyclohexane	1.5	1.4	1.5	230-231	(2) (3)
205	3-methylphenyl	1.5	1.3	1.5	238-241	
206	4-pyridyl	1.5	1.6	1.3	236-238	(4)

Notes

(1) Filtrate evaporated under reduced pressure. The residue was dissolved in dichloromethane, washed and dried and then loaded on to a Florisil® column. The product was obtained on elution with dichloromethane.

(2) Reaction mixture washed, dried and evaporated.

(3) Residue washed, triturated with ether and filtered to give the solid product.

(4) Pyridine (0.4 ml) was included with the starting materials in the reaction mixture. On filtration, the solid collected was triturated with triethylamine/water (1:6), filtered and washed with isopropanol and ether to give the product.

(5) The product obtained on evaporating off the solvent, was heated in boiling ethyl acetate.

(6) The solid collected after filtration was triturated with water/triethylamine (6:1), then filtered to give the product.

Examples 207-220

In a similar manner to that described in Example 187 a compound of formula I was prepared by reacting a compound of formula II' (the Example for the preparation of the starting ester is provided) with the appropriate acyl chloride ($R_{17}COCl$) as summarised in Table 15 below.

Table 15

Example	Prep. Example of II'	R_{17}	Amount of Reactants: II' (g)	$R_{17}COCl$ (ml)	Et_3N (ml)	m.p. of I (°C)	Notes
207	48	benzyl	1.5	1.2	1.2	147-150	(12)
208	48	methoxymethyl	1.5	0.9	1.2	120-122	(2) (3)
209	48	2-methoxycarbonylethyl	2.0	1.2	1.6	142-145	(2) (3) (13)
210	65	acetoxymethyl	2.4	1.6g	2.1	184-185	(1)
211	64	acetoxymethyl	0.8	0.6	0.7	189-191	(2) (3)
212	63	methoxymethyl	0.8	0.5	0.6	219-221	(4) (6) (7)
213	63	methylthioethyl	1.0	0.9g	0.9	201-203	(2) (5)
214	63	acetoxymethyl	0.8	0.5	0.6	223-224	(2) (6)
215	63	2-methoxycarbonylethyl	1.5	1.1	0.9g	182-184	(2) (7)

Table 15 cont'd

Example	Prep. Example of II'	R_{17}	Amount of Reactants: II' (g)	Amount of Reactants: $R_{17}COCl$ (ml)	Amount of Reactants: Et_3N (ml)	m.p. of I (°C)	Notes
216	66	methoxymethyl	2.0	1.2	1.9	124-126	(8)
217	140	acetoxymethyl	0.5	0.3	0.35	160-162	(9)
218	141	acetoxymethyl	1.3	0.7	0.9	114-116	(2) (3)
219	46	acetoxymethyl	2.0	1.2	1.5	161-163	(10)
220	66	2-methoxycarbonylethyl	2.0	1.6	1.9	182-184	(11)

Notes

(1) The reaction mixture was evaporated to dryness and the solid triturated with ethyl acetate and filtered. The solid collected was recrystallised from industrial methylated spirit.

(2) The reaction mixture was washed with water and evaporated to dryness.

(3) The product obtained was triturated with ether.

(4) Further portions of acyl chloride (0.2 ml) and triethylamine (0.3 ml)were added after twelve hours and the reaction mixture stirred for a further three hours at ambient temperature. The reaction mixture was washed, dried and concentrated to give a solid.

(5) The solid was purified by flash chromatography on silica using dichloromethane as the mobile phase. The product was recrystallised from ethyl acetate.

(6) The solid was washed with aqueous triethylamine and filtered and washed with water, isopropyl alcohol and ether.

(7) The solid product was recrystallised from ethyl acetate.

(8) The reaction mixture was filtered and the product was recrystallised from dioxan.

(9) The reaction mixture was added to ether, filtered and the filtrate evaporated to dryness and recrystallised from industrial methylated spirit.

(10) The reaction mixture was washed with dilute hydrochloric acid, water, then dried and evaporated. The solid obtained was recrystallised from propan-2-ol.

(11) Recrystallised from acetonitrile.

(12) Further portions of acyl chloride (0.6 ml) and triethylamine (0.6 ml) were added after 20 hours. An oil obtained on evaporating off the solvent was dissolved in dichloromethane, washed with dilute hydrochloric acid and water, dried and evaporated to give a gum which yielded the product on trituration with ether.

(13) Compound softens at 129°C.

Example 221

A solution of 2-(4-chlorophenyl)-8-hydroxy-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one (1.95 g) (Example 62) in dry pyridine (58 ml) was stirred in an ice-bath and treated with methyl succinyl chloride (1.6 ml). The reaction mixture was allowed to warm up to ambient temperature over 18 hours and then stirred at ambient temperature for a further 24 hours. The reaction mixture was added to water and extracted with ethyl acetate. The combined organic extracts were washed with water, dried and evaporated under reduced pressure. The residue was dissolved in dichloromethane and loaded on to a dry-packed Florisil® column. The column was eluted with dichloromethane/acetone (99:1). The required fractions were evaporated and the residue was triturated with ether to give 2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl methyl succinate, m.p. 152-153°C.

Examples 222-225

In a similar manner to that described in Example 221 a compound of formula I was prepared by reacting 2-(4-chlorophenyl)-8-hydroxy-4-methyl[1]benzopyrano-[4,3-c]-pyrazol-3(2H)-one (II') (Example 62) with the appropriate acid chloride, $R_{17}COCl$, as summarised in Table 16. In Examples 223, 224 and 225 more acid chloride was added and the mixture stirred for an additional period of time as shown.

Table 16

Example	R_{17}	Amount of Reactants: $R_{17}COCl$ (ml)	II' (g)	Pyridine (ml)	Time (hours)	m.p. of I (°C)	Notes
222	$CH_3CO_2CH_2$	1.8	2.25	68	18	193-195	(1)
223	$CH_3S(CH_2)_2$	1.7	2.25	65	18		
		0.9			24	159-162	(2)
224	$C_2H_5O_2C(CH_2)_2$	2.15	2.25	65	18		
		0.2			24	154-156	(1)
225	Ph	1.4	2.00	60	18		
		1.4			2	248-251	(3)

(1) The column was eluted with dichloromethane.
(2) Some of the crude product was insoluble in dichloromethane and this material was removed by filtration. The column was eluted with dichloromethane and then dichloromethane/acetone, 99:1.
(3) Material insoluble in the ethyl acetate/water mixture was collected by filtration and dried to give the product directly without chromatography.

Example 226

A stirred mixture of 2-(4-chlorophenyl)-9-hydroxy-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one (2 g) (Example 66) and pyridine (20 ml) was treated with benzoyl chloride (0.8 ml) and stirred for 48 hours at ambient temperature. The reaction mixture was poured into water and filtered. The solid obtained was recrystallised from toluene to give 2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano-[4,3-c]pyrazol-9-yl benzoate, m.p. 218-222°C.

Example 227

A solution of 2-(4-chlorophenyl)-8-hydroxy-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one (Example 62) (1.5 g) and nicotinoyl chloride hydrochloride (1.6 g) in a mixture of pyridine (45 ml) and triethylamine (2.55 ml) was stirred at ambient temperature for 18 hours. The mixture was left standing at ambient temperature for 48 hours then added to water and this mixture filtered to give 2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano-[4,3-c]pyrazol-8-yl nicotinate, m.p. 230-235°C.

Example 228

A mixture of 2-(4-chlorophenyl)-8-hydroxy-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one (Example 62) (1.8 g) and 4-methoxybenzyl hydrogen malonate (2.0 g) in dry pyridine (18 ml) was stirred in a cold water-bath. 1,3-dicyclohexylcarbodiimide (1.6 g) was added in portions over 5 minutes. The mixture was stirred at ambient temperature for 18 hours and then poured on to water. This mixture was extracted with ethyl acetate and the combined organic extracts washed

with water, dried and evaporated. The residue was triturated with ether and the solid collected by filtration then stirred with dichloromethane. After removing some insoluble material by filtration the dichloromethane solution was added to a Florisil® column. Elution with dichloromethane gave a solid which was triturated with ether and filtered to give 2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 4-methoxybenzyl malonate, m.p. 162-163°C.

Example 229

2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazol-8-yl 4-methoxybenzyl malonate (Example 228) (0.7 g) was stirred with dichloromethane (3 ml) in an ice-bath and treated with anisole (0.14 ml) and trifluoroacetic acid (1.54 ml). The solution was stirred at 0°C for 2.5 hours then washed with water whereupon a solid separated. The solid was collected by filtration, washed with dichloromethane and dried to give 2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl hydrogen malonate, m.p. 166°C.

Example 230

In a similar manner to Example 227, a mixture of 2-(4-chlorophenyl)-8-hydroxy-4-methyl[1]benzopyrano-[4,3-c]pyrazol-3(2H)-one (Example 62) (1.5 g), N,N-dimethylglycine (0.78 g) and dry pyridine (15 ml) was stirred at ambient temperature. 1,3-dicyclohexylcarbodiimide (1.35 g) was added and the reaction mixture stirred at ambient temperature for 2 days to give, after chromatography using dichloromethane/acetone (99:1) as the mobile phase, 2-(4-chlorophenyl)-

4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c] pyrazol-8-yl dimethylaminoacetate, m.p. 174-176°C.

Example 231

In a similar manner to Example 227, a stirred mixture of 2-(4-chlorophenyl)-8-hydroxy-4-methyl[1]-benzopyrano[4,3-c]pyrazol-3-(2H)-one (Example 62) (1.5 g), methylthioacetic acid (0.6 ml) and dry pyridine (15 ml) was treated with 1,3-dicyclohexyl-carbodiimide (1.35 g) at ambient temperature. The mixture was stirred at ambient temperature for 2 days to give, after chromatography, 2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl methylthioacetate, m.p. 163-166°C.

Example 232

A mixture of ethyl 2-(4-chlorophenyl)-8-hydroxy-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate (2.0 g) (Example 48) in dry dichloromethane (60 ml) was stirred at 0°C while triethylamine (1.6 ml) was added followed by acetoxyacetyl chloride (1.2 ml). The mixture was allowed to warm up to ambient temperature during 30 minutes then washed with water, dried and evaporated. The solid residue was triturated with ether and filtered to give ethyl 3,8-di(acetoxy-acetoxy)-2-(4-chlorophenyl)-2,4-dihydro[1]benzopyrano-[4,3-c]pyrazol-4-ylideneacetate which on standing in air hydrolysed to ethyl 8-acetoxyacetoxy-2-(4-chloro-phenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate hemihydrate containing one mole of acetoxy-acetic acid, m.p. 157-160°C.

Example 233

A stirred mixture of 2-(3,4-dichlorophenyl)-8-hydroxy-3a-methyl-3a,4-dihydro[1]benzothiopyrano[4,3-c]pyrazol-3(2H)-one (1.50 g), (Example 73) triethylamine (0.61 ml) and dichloromethane (30 ml) was treated dropwise with ethyl malonyl chloride (0.56 ml). The mixture was stirred at ambient temperature for 2 hours and then evaporated under reduced pressure. The residue was partitioned between ether (50 ml) and water (50 ml). The organic layer was separated and the aqueous layer extracted with ether. The combined ether extracts were dried and evaporated to give a solid which was recrystallised from ethyl acetate to give 2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl ethyl malonate, m.p. 139-141°C.

Examples 234-251

In a similar manner to that described in Example 233, a compound of formula I was prepared by reacting a compound of formula I' (preparative Example of starting compound provided) with an acyl chloride $R_{17}COCl$ as summarised in Table 17 below. In each case dichloromethane (30 ml) was used.

Table 17

Ex	Ex of Starting Cpd I'	R_{17}	Amounts of Reactants: I' (g)	$R_{17}COCl$ (ml)	NEt_3 (g)	Reaction Time (hours)	m.p.of I (°C)	Notes
234	73	methoxymethyl	1.3	0.4	0.5	2	119-121	
235	73	acetoxymethyl	1.5	0.5	0.6	2	159-160	(1a)
236	73	benzyl	1.3	0.8	0.8	2	49-51	
237	73	phenyl	1.5	0.5	0.6	2	163-164	(2)
238	73	methoxycarbonylmethyl	1.3	0.5	0.5	2	119-121	
239	73	1-propylene	1.1	0.3	0.5	1.5	124-125	(1b)
240	73	ethyl	0.8	0.2	0.3	2	131-132	(1b) (3)
241	76a	acetoxymethyl	0.8	0.3	0.3	40	188-189	(4)
242	72	acetoxymethyl	0.9	0.3	0.4	1	134-136	(1c)
243	74	methoxymethyl	1.1	0.3	0.5	1	165-167	(1d)
244	75	acetoxymethyl	0.8	0.4	0.3	1	122-124	(1e)
245	75	ethoxycarbonylmethyl	0.8	0.4	0.4	2	95-97	(1c)
246	72	methoxymethyl	0.9	0.2	0.4	1	102-105	(1c) (1b)
247	75	methoxymethyl	0.8	0.2	0.4	1	111-114	(1c)

Table 17 Cont'd

Ex	Ex of Starting Cpd I'	R_{17}	Amounts of Reactants			Reaction Time	m.p.of I	Notes
			I' (g)	$R_{17}COCl$ (ml)	NEt_3 (g)	(hours)	(°C)	
248	74	acetoxymethyl	0.8	0.3	0.5	1	130-135	(1c)
249	73	ethoxycarbonylmethyl	1.1	0.3	0.4	1.5	95-97	(5) (1f)
250	76	acetoxymethyl	0.7	0.5	0.6	2	218-219	(5) (1e)
251	76	ethylcarbonylmethyl	0.9	0.5	0.6	4	146-147	(1c)

Ex = Example; NEt_3 = triethylamine

Notes

(1) Recrystallisation from:-

a) ether
b) ethanol
c) ethyl acetate/petroleum ether (b.p. 60-80°C)
d) methanol
e) ethyl acetate
f) isopropanol;

(2) The ether extracts were evaporated and then water added to the residue. Extraction with ethyl acetate followed by 2 recrystallisations from ethyl acetate gave the product.

(3) A further equivalent portion of triethylamine and acyl chloride was added after 1 hour.

(4) N,N-dimethyl formamide (2 ml) was added to the reaction mixture initially. A further portion of triethylamine (0.3 ml) and acetoxyacetyl chloride (0.3 ml) was added after 16 hours.

(5) Purification of crude product by flash chromatography on silica using dichloromethane as the mobile phase.

The following compounds have a chiral carbon atom and may exist in R- and S- enantiomeric forms:-

Examples 111, 133, 149, 151, 152, 153

Example 252

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled

into hard gelatin capsules, each capsule containing 10 mg active compound.

Example 253

In the preparation of capsules, 50 parts by weight of active compound, 300 parts by weight of lactose and 3 parts by weight of magnesium stearate are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule contianing 50 mg of active ingredient.

Example 254

Tablets are prepared from the following ingredients.

	Parts by weight
Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinylpyrrolidone in ethanol. The dry granulate is blended with magnesium stearate and the rest of the starch. The mixture is then compressed in a tableting machine to give tablets containing:

a) 10 mg
b) 100 mg
c) 500 mg

of active compound.

Example 255

Tablets are prepared by the method of Example 254. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

Example 256

In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of semi-synthetic glycerides as the suppostiroy base and the mixture formed into suppositories each containing 100 mg of active ingredient.

Example 257

In the preparation of ointments the active compound is incorporated into the base by thorough homogenization until the drug is evenly distributed. The ointment is packed into 10 g amber jars with screw-capped lined lids.

Active compound	0.1 g
White soft paraffin to	10 g

The compounds of the invention are immunomodulatory agents, especially immunosuppressants and may show therapeutic activity at a dose of 200 mg/kg or lower. Preferred compounds of the invention show activity at 50 mg/kg or lower. The therapeutic activity of the preferred compounds of the present invention has been demonstrated by a cutaneous hypersensitivity test (CH test) in which the compounds are administered parenterally to BALB/c mice. This test was carried out in the following way.

Female BALB/c mice, weight range 16-24 g, were used in groups of eight. The abdomen of each mouse was shaved and 20 µl of a solution of a sensitising agent, 5% w/v 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (oxazolone) in acetone:ethanol (1:1 by volume), was applied to the shaved area. Immediately after sensitisation, the test compound in one of the dosages listed below was injected intraperitoneally as a suspension in 1.5% v/v sorbitan esters, under the trade name Tween 80, in sterile water (100 µl). 100 µl of the same suspension was injected likewise every 24 hours for a further 7 days. The dosages used were selected from the following values: 50, 30, 10, 3, 1, 0.3, 0.1, 0.03 or 0.01 mg/kg.

Two groups of at least eight BALB/c mice were used as a control simultaneously with each test in a similar manner to that described above except that no test compound was included in the daily injections.

On the seventh day after sensitisation, 10 µl of a solution of 1% w/v oxazolone in acetone: olive oil (3:1 by volume) was applied to one ear (the challenged ear) of each of the test mice and the control mice. (A more potent challenge dose of 1.5% w/v oxazolone in acetone:olive oil was employed in a few cases). After 24 hours the thickness of the challenged ear and the thickness of the non-challenged ear of the same animal were measured with an engineer's screw gauge micrometer. The difference in thickness between the challenged ear and the non-challenged ear in each animal is a measure of the response of that animal to oxazolone. A comparison between the response of mice treated with the test compound and mice treated with the control indicates the effectiveness of the test compound as an immunomodulatory agent. The compounds were considered to be active at a particular dose if a

20% or greater reduction in ear swelling, which was statistically significant ($p < 0.05$) according to Dunnett's test, between treated and control groups was obtained in at least two out of three CH tests, (or, where more than three tests have been carried out, a majority of the tests) at that dose (see for example Int. Arch. Allergy, 38, p246-259 (1970)).

Each of the compounds of formula I illustrated in Table A below was active at 50 mg/kg in at least two out of three tests at 50 mg/kg unless indicated otherwise (see Notes following the Table). The minimum effective dose for each compound is given in Table A. The Example (Ex) number or numbers listed adjacent to each compound indicates the process or processes illustrating the preparation of that compound in the Examples.

Table A

Ex	Compound Name	Minimum Effective Dose (mg/kg)
77	4-methyl-2-(5-trifluoromethyl-2-pyridyl)[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	3
78	2-(5-chloro-2-pyridyl)-4-methyl[1]-benzopyrano[4,3-c]pyrazol-3(2H)-one	3
79	2-(6-chloro-2-pyridyl)-4-methyl[1]-benzopyrano[4,3-c]pyrazol-3(2H)-one	50
80	4-methyl-2-(6-trifluoromethyl-2-pyridyl)-[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	50
81	2-(4-chloro-2-pyridyl)-4-methyl[1]-benzopyrano[4,3-c]pyrazol-3(2H)-one	≤3
82	2-(6-chloro-5-trifluoromethyl-2-pyridyl)-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	3
83	2-(5-bromo-2-pyridyl)-4-methyl[1]-benzopyrano[4,3-c]pyrazol-3(2H)-one	50
84	2-(5-chloro-2-pyridyl)-9-hydroxy-4-methyl[1]benzopyrano[4,3-c]-pyrazol-3(2H)-one	50
85	8-fluoro-4-methyl-2-(5-trifluoro-methyl-2-pyridyl)[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	≤50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
86	2-(5-chloro-2-pyridyl)-8-fluoro-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	50
87	2-(5-chloro-2-pyridyl)-4-methylthiomethyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	50
88	ethyl 2-(5-chloro-2-pyridyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3(a)
89	2-(5-chloro-2-pyridyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-9-yl acetate	≤3(a)
90	2-(5-chloro-2-pyridyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
91	2-piperidinoethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate hydrochloride 0.4 hydrate	50
92	3-(4-methyl-1-piperazinyl)propyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate 2.5 hydrochloride dihydrate	50
93	2-morpholinoethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate hydrochloride hemihydrate	≤3
94	2-morpholinoethyl 2-(3,4-dichlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	≤50
95	2-morpholinoethyl 2-(4-chlorophenyl)-8-hydroxy-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	50
96	3-morpholinopropyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate hydrochloride monohydrate	≤3
97	2-morpholinoethyl 2-(4-bromophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate hydrochloride hemihydrate	≤50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
98	2-morpholinoethyl 2-(4-fluorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate hydrochloride	≤50
99	2-morpholinoethyl 2-(4-chlorophenyl)-8-fluoro-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate hydrochloride 0.4 hydrate	≤50
100	2-morpholinoethyl 2-(4-chlorophenyl)-9-methoxy-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate hydrochloride	50
101	4-methoxybenzyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤1
102	benzyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	≤3
103	phenethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	≤3
104	cyclopentyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3

Ex	Compound Name	Minimum Effective Dose (mg/kg)
105	2-methoxyethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
106	2-(2-thienyl)ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
107	cyclobutylmethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	3
108	2-(2-pyridyl)ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	50
109	cyclobutyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
110	2-(2-methoxyethoxy)ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	≤3
111	tetrahydrofurfuryl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
112	tetrahydro-2H-pyran-4-yl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	≤3

Ex	Compound Name	Minimum Effective Dose (mg/kg)
113	2-(4-methyl-5-thiazolyl)ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate	≤3
114	3-methoxybenzyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
115	4-methylbenzyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
116	4-methoxyphenethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
117	4-chlorophenethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
118	2-chlorobenzyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
119	3-oxobutyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
120	2-chlorophenethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
121	3-methylphenethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
122	cyclohexyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
123	3-chlorobenzyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
124	3-hydroxypropyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	50
125	2-phenoxyethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano-[4,3-c]pyrazole-4-acetate	≤50
126	4-dimethylaminophenethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	≤50
127	2-acetamidoethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
128	3-methylbenzyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
129	2-methylbenzyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
130	4-chlorobenzyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
131	2-methoxybenzyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	≤50
132	3-(3-pyridyl)propyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
133	α-methylphenethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	≤50
134	cyclopropylmethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
135	cyclobutylmethyl 3-oxo-2-(4-trifluoro-methylphenyl)-2,3-dihydro[1]benzopyrano-[4,3-c]pyrazole-4-acetate	≤50
136	cyclobutylmethyl 2-(4-chlorophenyl)-8-methyl-3-oxo-2,3-dihydro[1]benzopyrano-[4,3-c]pyrazole-4-acetate	≤50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
137	cyclobutylmethyl 2-(4-methoxyphenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
138	cyclobutylmethyl 2-(4-methylphenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
139	cyclobutylmethyl 2-(3-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
140	cyclobutylmethyl 2-(4-chlorophenyl)-9-hydroxy-3-oxo-2,3-dihydro[1]benzopyrano-[4,3-c]pyrazole-4-acetate	≤50
142	2-acetoxyethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
143	2-hydroxyethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
144	2-thiomorpholinoethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate hydrochloride	≤3
145	2-methylthioethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3

Ex	Compound Name	Minimum Effective Dose (mg/kg)
146	4,4,4-trifluorobutyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	50
147	2-cyanoethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
148	2-ethoxycarbonylethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	50
149	β-methylphenethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	≤50
150	2-cyclohexylethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤3
151	1-methyl-2-morpholinoethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	50
152	1-methyl-2-piperidylmethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate	50
153	2-morpholinoethyl 2-(4-chlorophenyl)-3-oxo-1,2,3,4-tetrahydro[1]benzopyrano-[4,3-c]pyrazole-4-acetate	50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
154	3-acetoxypropyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	≤50
155	2-(4-chlorophenyl)-N-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetanilide	50
156	N-benzyl-2-(4-chlorophenyl)-N-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetamide	50
157	2-(4-chlorophenyl)-N-methyl-N-(2-morpholinoethyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetamide	50
158	2-(4-chlorophenyl)-N-methyl-3-oxo-N-(3-pyridylmethyl)-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetamide	50
159	2-(4-chlorophenyl)-N-ethyl-3-oxo-N-phenyl-2,3-dihydro[1]benzopyrano-[4,3-c]pyrazole-4-acetamide	3
160	N-benzyl-2-(4-bromophenyl)-N-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetamide	50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
161	N-benzyl-2-(3,4-dichlorophenyl)-N-methyl-3-oxo-2,3-dihydro[1]benzopyrano-[4,3-c]pyrazole-4-acetamide	50
162	N-benzyl-2-(4-chlorophenyl)-8-fluoro-N-methyl-3-oxo-2,3-dihydro[1]benzo-pyrano[4,3-c]pyrazole-4-acetamide	50
163	2-(4-chlorophenyl)-N-methyl-3-oxo-N-phenethyl-2,3-dihydro[1]benzopyrano-[4,3-c]pyrazole-4-acetamide	50
164	2-(4-chlorophenyl)-N-(2-cyanoethyl)-N-methyl-3-oxo-2,3-dihydro[1]benzo-pyrano[4,3-c]pyrazole-4-acetamide	50
165	2-(4-chlorophenyl)-N,N-(3-oxapenta-methylene)-3-oxo-2,3-dihydro[1]benzo-pyrano[4,3-c]pyrazole-4-acetamide	50
166	4'-chloro-2-(4-chlorophenyl)-N-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetanilide	50
167	N-benzyl-2-(4-fluorophenyl)-N-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetamide	50
168	2-(4-chlorophenyl)-N-(1,3-dioxolan-2-ylmethyl)-N-methyl-3-oxo-2,3-dihydro-[1]benzopyrano[4,3-c]pyrazole-4-acetamide	50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
169	methyl 4-[2-(4-chlorophenyl)-N-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetamido]benzoate	50
170	2-{4-[2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetyl]piperazin-1-yl}ethyl acetate	50
171	2-{4-[2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetyl]piperazin-1-yl}ethyl propionate	50
172	N,N-(3-oxapentamethylene)-3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzothiopyrano[4,3-c]-pyrazole-4-acetamide	≤50
173	N-ethyl-3-oxo-N-phenyl-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]-benzothiopyrano[4,3-c]pyrazole-4-acetamide	≤50
174	methyl 5-[2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazol-4-yl]-4-oxopentanoate	50
175	2-(4-chlorophenyl)-4-(2-oxo-3-phenyl-propyl)[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
176	2-(4-chlorophenyl)-4-(2-oxo-3-phenoxypropyl)[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	3
177	2-(4-chlorophenyl)-4-(2-cyclohexyl-2-oxoethyl)[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	50
178	2-(4-chlorophenyl)-4-(2-cyclopropyl-2-oxoethyl)[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	50
179	2-(4-chlorophenyl)-4-[4-(4-methoxyphenyl)-2-oxobutyl][1]benzopyrano[4,3-c]pyrazol-3(2H)-one	≤50
180	4-[3-(4-chlorophenoxy)-2-oxopropyl]-2-(4-chlorophenyl)[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	≤3
181	2-(4-chlorophenyl)-4-[4-(3-methylphenyl)-2-oxobutyl][1]benzopyrano-[4,3-c]pyrazol-3(2H)-one	≤50
182	2-(4-chlorophenyl)-4-(3-cyclopentyl-2-oxopropyl)[1]benzopyrano[4,3-c]-pyrazol-3(2H)-one	≤50
183	2-(4-chlorophenyl)-4-[3-(2-methylphenoxy)-2-oxopropyl][1]benzopyrano-[4,3-c]pyrazol-3(2H)-one	≤50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
184	2-(4-chlorophenyl)-4-(4-methylthio-2-oxobutyl)[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	≤50
185	2-(3,4-dichlorophenyl)-4-(2-oxo-3-phenoxypropyl)[1]benzopyrano[4,3-c]-pyrazol-3(2H)-one	≤50
186	2-(4-chlorophenyl)-4-(3-methoxy-2-oxo-propyl)[1]benzopyrano[4,3-c]pyrazol-3-(2H)-one	≤3(a)
187	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-9-yl methyl malonate	≤3
188	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl ethyl malonate	≤1
189	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl methoxyacetate	≤3(a)
190	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl cyclopropanecarboxylate	50
191	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 1-adamantanecarboxylate	≤3

Ex	Compound Name	Minimum Effective Dose (mg/kg)
192	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 3-phenylpropionate	50
193	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl phenylacetate	50
194	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 2-methoxybenzoate	50
195	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 2-furoate	50
196	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 2-thenoate	50
197	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl cyclobutanecarboxylate	$\leq$3
198	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 2-methylbenzoate	$\leq$50
199	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 4-chlorobenzoate	$\leq$50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
200	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazol-8-yl crotonate	50
201	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazol-8-yl 4-methoxybenzoate	≤50
202	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazol-8-yl 4-methylbenzoate	≤50
203	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazol-8-yl cyclopentanecarboxylate	50
204	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazol-8-yl cyclohexanecarboxylate	50
205	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 3-methylbenzoate	50
206	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl isonicotinate	≤50
207	Ethyl 2-(4-chlorophenyl)-3-oxo-8-phenylacetoxy-2,3-dihydro[1]benzo-pyrano[4,3-c]pyrazole-4-acetate	50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
208	Ethyl 2-(4-chlorophenyl)-8-methoxyacetoxy-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate 0.3 methoxyacetic acid solvate	50
209	2-(4-chlorophenyl)-4-ethoxycarbonylmethyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl methyl succinate	50
210	4-methyl-3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl acetoxyacetate	≤50
211	2-(4-bromophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl acetoxyacetate	≤50
212	2-(3,4-dichlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl methoxyacetate	≤50
213	2-(3,4-dichlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazol-8-yl 3-(methylthio)propionate	≤50
214	2-(3,4-dichlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazol-8-yl acetoxyacetate	50
215	2-(3,4-dichlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazol-8-yl methyl succinate	≤50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
216	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazol-9-yl methoxyacetate	50
217	cyclobutylmethyl 9-acetoxyacetoxy-2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate	≤50
218	cyclobutylmethyl 8-acetoxyacetoxy-2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate 0.5 hydrate, 0.35 acetoxyacetic acid solvate	≤50
219	Isopropyl 8-acetoxyacetoxy-2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazole-4-acetate 0.2 hydrate, 0.5 acetoxyacetic acid solvate	≤50
220	2-(4-chlorophenyl)-4-methyl-3-oxo-,2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-9-yl methyl succinate	≤3
221	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl methyl succinate	≤1
222	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl acetoxyacetate	≤1

Ex	Compound Name	Minimum Effective Dose (mg/kg)
223	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 3-(methylthio)propionate	3
224	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl ethyl succinate	50
225	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl benzoate	3
226	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-9-yl benzoate	50
227	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl nicotinate	50
228	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 4-methoxybenzyl malonate	50
229	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl hydrogen malonate	50
230	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl dimethylaminoacetate	≤3

Ex	Compound Name	Minimum Effective Dose (mg/kg)
231	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl (methylthio)acetate	50
232	ethyl 8-acetoxyacetoxy-2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate hemihydrate acetoxyacetic acid solvate	3
233	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl ethyl malonate	≤3
234	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl methoxyacetate	≤3
235	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl acetoxyacetate	≤3
236	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl phenylacetate	≤3
237	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl benzoate	≤1

Ex	Compound Name	Minimum Effective Dose (mg/kg)
238	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl methyl succinate	≤1
239	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl crotonate	≤50
240	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl propionate	≤50
241	2-(3,4-dichlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzothiopyrano-[4,3-c]pyrazol-8-yl acetoxyacetate	50
242	3a-methyl-3-oxo-2-(4-trifluoromethylphenyl)-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl acetoxyacetate	≤50
243	2-(4-chlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano-[4,3-c]pyrazol-8-yl methoxyacetate	≤50
244	2-(4-fluorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]-pyrazol-8-yl acetoxyacetate	≤50

Ex	Compound Name	Minimum Effective Dose (mg/kg)
245	Ethyl 2-(4-fluorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano-[4,3-c]pyrazol-8-yl malonate	≤50
246	3a-methyl-3-oxo-2-(4-trifluoromethylphenyl)-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl methoxyacetate	≤3
247	2-(4-fluorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano-[4,3-c]pyrazol-8-yl methoxyacetate	50
248	2-(4-chlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano-[4,3-c]pyrazol-8-yl acetoxyacetate	≤50
249	Ethyl 3a-methyl-3-oxo-2-(4-trifluoromethylphenyl)-2,3,3a,4-tetrahydro[1]-benzothiopyrano[4,3-c]pyrazol-8-yl malonate	≤50
250	4-Methyl-3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzothiopyrano-[4,3-c]pyrazol-8-yl acetoxyacetate	≤50
251	Ethyl 4-methyl-3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl malonate	≤50

Notes:

(a) Active in each of two tests at 3 mg/kg

The compounds of the present invention also show activity in a variety of other in-vivo screens, which show the utility of the compounds as immunomodulants, particularly in suppressing the immune response. Administration of the compounds has been carried out orally or parenterally. Some compounds have been found to be active in a test which determines their effects on humoral immunity by assaying the sera collected at the end of the oxazolone induced cutaneous hypersensitivity test described above (CH test) for changes in the amount of anti-oxazolone antibody produced, and a Graft versus Host test similar to that used by Smith S R, Terminelli C, Kipilman C T and Smith Y., J. Immunopharmacology 1981;3(2),133-170.

For example, the compounds prepared in the following Examples were also found to be active in the above-described antibody test after parenteral administration at 50 mg/kg. A compound was deemed to be active, if at a dose of 50 mg/kg it caused a decrease in the relative serum anti-oxazolone antibody concentration determined by an enzyme linked immunosorbent assay (ELISA) by a factor of 0.5 or greater calculated by the following formula:-

$$\frac{O.D.(C_1) - O.D.(T_1)}{O.D.(C_1) - O.D.(C_2)}$$

where $O.D.(C_1)$ is the optical density of the control serum at a dilution of 1/128

$O.D.(C_2)$ is the optical density of the control serum at a dilution of 1/256

$O.D.(T_1)$ is the optical density of the test serum at a dilution of 1/128

The control and test sera were diluted with phosphate buffered saline (pH 7.3) containing 0.05% v/v Tween 20 (trade name).

Compounds active in above test:

Examples 77-79, 81-137, 139-140, 142-159, 161, 164, 166-7, 169-197, 199-240, 242-251.

The following compounds were active at or below 50 mg/kg as defined herein and were prepared in an analogous manner to those described herein:

Ex	Compound Name	Melting Point(°C)
258	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 4-morpholinomethylbenzoate	115-188 (dec)
259	methyl 5-[3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzothiopyrano-[4,3-c]pyrazol-4-yl]-4-oxopentanoate	140-143
260	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano-[4,3-c]pyrazol-8-yl 2-thenoate	191-193
261	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano-[4,3-c]pyrazol-8-yl nicotinate	149-150
262	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano-[4,3-c]pyrazol-8-yl 3-methylbenzoate	132-135
263	ethyl 2-(5-chloro-2-pyridyl)-8-hydroxy-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	258-265 (dec)

Ex	Compound Name	Melting Point (°C)
264	2-(2-methylpiperidino)ethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano-[4,3-c]pyrazole-4-acetate hydrochloride	210-213
265	2-[4,5-bis(trifluoromethyl)-2-pyridyl]-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	235-238
266	2-(5-chloro-2-pyridyl)-N-ethyl-3-oxo-N-phenyl-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetamide	181-184
267	cyclobutylmethyl 2-(5-chloro-2-pyridyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]-pyrazole-4-acetate	157-160
268	4-[3-(3-chlorophenoxy)-2-oxopropyl]-2-(4-chlorophenyl)[1]benzopyrano[4,3-c]-pyrazol-3(2H)-one	193-195
269	4-[3-(2-chlorophenoxy)-2-oxopropyl]-2-(4-chlorophenyl)[1]benzopyrano[4,3-c]-pyrazol-3(2H)-one	215-217
270	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 4-(4-methylpiperazin-1-ylmethyl)-benzoate hydrochloride hydrate	153-156
271	4-methoxybenzyl 2-(3,4-dichlorophenyl)-3-oxo-2,3-dihydro[1]benzothiopyrano-[4,3-c]pyrazole-4-acetate	188-190

Ex	Compound Name	Melting Point (°C)
272	2-acetoxyacetoxyethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate	131
273	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl 4-diethylaminomethylbenzoate	147-151
274	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl glycinate (0.9) hydrochloride	305-310 (dec)
275	4-(2-oxo-3-phenylpropyl)-2-(4-trifluoromethylphenyl)[1]benzothiopyrano[4,3-c]-pyrazol-3(2H)-one	173-175
276	4-methoxybenzyl 3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzothiopyrano[4,3-c]pyrazole-4-acetate	137-138
277	2-(5-chloro-2-pyridyl)-9-methoxy-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	254-256
278	2-(4-chlorophenyl)-4-(4-methylsulphonyl-2-oxobutyl)[1]benzopyrano-[4,3-c]pyrazol-3(2H)-one	221-223
279	2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-8-yl tert-butoxycarboxamidoacetate	192-193

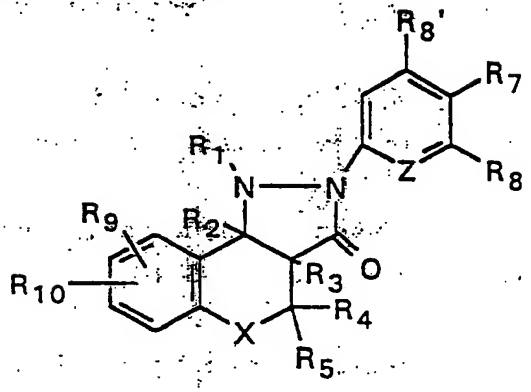
Ex	Compound Names	Melting Point (°C)
280	4-[3-(4-methoxyphenyl)-2-oxopropyl]-2-(4-trifluoromethylphenyl)[1]-benzothiopyrano[4,3-c]pyrazol-3(2H)-one	184-187
281	2-(4-chlorophenyl)-4-[3-(4-methoxyphenyl)-2-oxopropyl][1]benzopyrano-[4,3-c]pyrazol-3(2H)-one	178-180
282	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl 4-methoxybenzoate	141-142
283	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl 2-furoate	189-190
284	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl 4-chlorobenzoate	170-173
285	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl 3-(methylthio)propionate	97-99
286	2-(2-thienyl)ethyl 3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzothiopyrano[4,3-c]pyrazole-4-acetate	144-146

Ex	Compound Name	Melting Point (°C)
288	4-(2-oxo-3-phenoxypropyl)-2-(4-trifluoromethylphenyl)[1]benzothiopyrano[4,3-c]pyrazol-3(2H)-one	205-208
289	2-methoxyethyl 3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]benzothiopyrano[4,3-c]pyrazole-4-acetate	134-137
290	2-morpholinoethyl 3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]-benzothiopyrano[4,3-c]pyrazole-4-acetate	154-156
291	4-(3-methoxy-2-oxopropyl)-2-(4-trifluoromethylphenyl)[1]benzothiopyrano-[4,3-c]pyrazol-3(2H)-one	148-150
292	4-[2-oxo-3-(2-thienyl)propyl]-2-(4-trifluoromethylphenyl)[1]benzothiopyrano[4,3-c]pyrazol-3(2H)-one	169-179
293	Tetrahydro-2H-pyran-4-yl 3-oxo-2-(4-trifluoromethylphenyl)-2,3-dihydro[1]-benzothiopyrano[4,3-c]pyrazole-4-acetate	172-175
294	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-6-yl propionate	123-126
295	2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-6-yl acetoxyacetate	113

Ex	Compound Name	Melting Point (°C)
296	2-(4-chlorophenyl)-4-[2-oxo-3-(2-thienyl)propyl][1]benzopyrano[4,3-c]-pyrazol-3(2H)-one	135-138
297	2-(4-chlorophenyl)-N-cyclopropyl-N-cyclopropylmethyl-3-oxo-2,3-dihydro-[1]benzopyrano[4,3-c]pyrazole-4-acetate	160-162
298	2-(4-chlorophenyl)-4-[4-(2-chloro-phenyl)-2-oxobutyl][1]benzopyrano-[4,3-c]pyrazol-3(2H)-one	166-168
299	Cyclobutylmethyl 2-(4-chlorophenyl)-6-methoxy-3-oxo-2,3-dihydro[1]benzo-pyrano[4,3-c]pyrazole-4-acetate	164-166
300	N-Benzyl-2-(4-chlorophenyl)-N-cyclo-pentyl-3-oxo-2,3-dihydro[1]benzo-pyrano[4,3-c]pyrazole-4-acetamide	197-199
301	2-(5-Chloro-2-pyridyl)-6,8-difluoro-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one	218-223
302	Ethyl 4-methyl-3-oxo-2-(4-trifluoro-methylphenyl)-2,3-dihydro[1]benzo-thiopyrano[4,3-c[pyrazol-8-yl malonate	146-147

Claims

1. A compound of formula I



I

in which X represents oxygen or sulphur;

when X represents oxygen or sulphur R_1 represents hydrogen or together with R_2 represents a bond; R_2 together with either one of R_1 and R_3 represents a bond; R_3 together with either one of R_2 and R_4 represents a bond; R_4 represents hydrogen or together with R_3 represents a bond;

or when X represents sulphur, R_1 and R_2 represent a bond, R_3 represents methyl and R_4 and R_5 represent hydrogen;

Z represents -CH= or -N= when X represents oxygen;

Z represents -CH= when X represents sulphur;

R_5 represents hydrogen when R_3 represents methyl,

or R_5 represents $\underset{R_6}{CH} - R_6$,

when R_3 represents a bond together with either one of R_2 and R_4;

R_6 represents hydrogen, halo, $S(O)_nY_1$, carboxy, carbamoyl, a carboxylic acyl group, an esterified carboxyl group or $CONR_{12}R_{13}$;

$R_{6'}$ represents hydrogen or methyl;

or R_6 and $R_{6'}$ together with the carbon atom to which they are attached represent cyclopropyl;

R_7 represents hydrogen, halo, trifluoromethyl, C_{1-6} alkyl, methoxy or $S(O)_mY_1$;

R_8 represents hydrogen, halo or trifluoromethyl;

$R_{8'}$ represents hydrogen, halo or trifluoromethyl;

R_9 and R_{10}, which may be the same or different, represent halo; or R_9 represents hydrogen and R_{10} represents hydrogen, halo, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or a carboxylic acyloxy group;

R_{12} represents methyl, ethyl or C_{3-8} cycloalkyl and R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocylic group, a 5 or 6 membered heterocyclic aryl group or C_{3-8} cycloalkyl; or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or

R_{12} and R_{13} together with the nitrogen to which they are attached represent a 3-8 membered non-aromatic heterocylic group which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group;

Y_1 represents C_{1-6} alkyl;
n is 0, 1 or 2 and m is 0 or 1;

or a pharmaceutically acceptable salt thereof;
provided that:

I). when X is oxygen, Z is -CH= and:

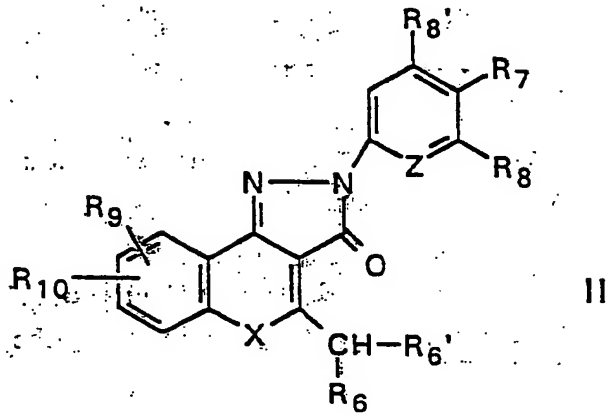
a) R_6 represents C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy; or

b) when R_6 represents hydrogen, halo, $S(O)_nY_1$, carbamoyl, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkanoyl or when R_6 and $R_{6'}$ together with the carbon atom to which they are attached form cyclopropyl then R_{10} represents a carboxylic acyloxy group other than C_{2-6} alkanoyloxy; or

c) when R_1 and R_2 form a bond, R_3 and R_4 form a bond, $R_{6''}$, R_8, $R_{8'}$, R_9 and R_{10} each represent hydrogen, R_7 represents chloro, then R_6 does not represent 4-methoxybenzyloxycarbonyl; or

II) When X is sulphur and a) R_3 represents methyl; or b) R_6 represents hydrogen, carboxy, $S(O)_nY_1$, C_{2-6} alkoxycarbonyl, carbamoyl, or C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy.

2. A compound according to claim 1 represented by formula II



II

in which R_6'represents hydrogen.

3. A compound according to either one of claims 1 and 2 wherein R_6 represents $CO_2(CH_2)_pJ$ in which p is 0-3 and J represents cyano, hydroxy, C_{3-8} cycloalkyl, C_{2-6} alkanoyloxy, C_{2-6} alkoxycarbonyl, C_{1-6} alkoxy, C_{1-6} alkoxy(C_{1-6})alkoxy, C_{1-6} alkylthio, or J represents a 5 or 6 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen; a 5 or 6 membered aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen or a carbocyclic aryl group, each of which groups is optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halo.

4. A compound according to either one of claims 1 and 2 wherein R_6 represents $CO_2NR_{12}R_{13}$ in which R_{12} represents ethyl and R_{13} represents phenyl.

5. A compound according to either one of claims 1 and 2 wherein R_6 represents $COCH_2K$ in which K represents C_{1-4} alkoxy or phenoxy.

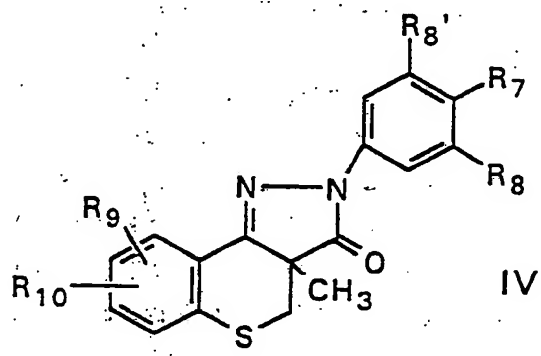
6. A compound according to any one of claims 1 to 5 in which R_{10} represents hydrogen, hydroxy, halo, C_{1-6} alkoxy or C_{1-6} alkyl.

7. A compound according to any one of the preceding claims in which R_{10} represents $OCO(CH_2)_pL$ in which p is 0-3 and L represents hydrogen, C_{3-11} cycloalkyl; di(C_{1-6} alkyl)amino; C_{2-6} alkanoyloxy; C_{2-6} alkoxy-carbonyl, C_{1-6} alkylthio; C_{1-6} alkoxy; adamantyl or phenyl optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halo.

8. A compound according to claim 7 in which R_{10} is substituted in the 8- or 9- position.

9. A compound according to either one of claims 7 and 8 in which R_6 represents hydrogen or C_{2-6} alkoxycarbonyl and R_6' represents hydrogen.

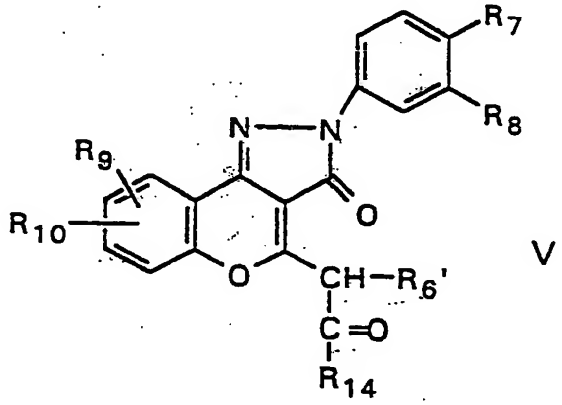
10. A compound according to claim 1 represented by formula IV



IV

in which R_7 represents halo or trifluoromethyl, R_8 represents hydrogen or halo, R_8' represents hydrogen or halo and R_9 represents hydrogen.

11. A compound according to claim 1 represented by formula V

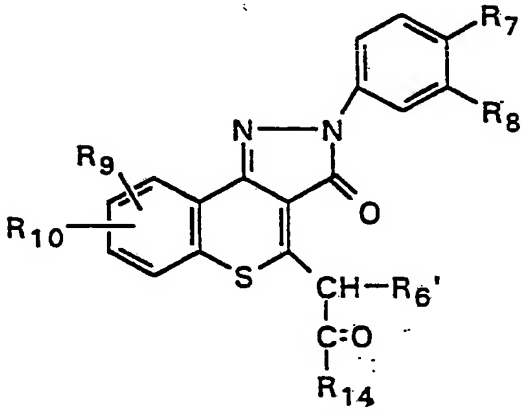


V

in which R_6' represents hydrogen, R_{14} represents OR_{15}, R_{16} or $NR_{12}R_{13}$ in which R_{12} represents methyl or ethyl, R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen, a 5 or 6 membered heterocyclic aryl group containing 1 to 3 heteroatoms

selected from oxygen, sulphur or nitrogen or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or R_{12} and R_{13} together with nitrogen to which they are attached form a 3-8 membered non-aromatic heterocyclic ring which may contain a further heteroatom selected from oxygen, sulphur or nitrogen which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group; and R_{15} and R_{16}, which may be the same or different, represent optionally substituted groups selected from C_{1-6} alkyl; C_{2-6} alkenyl; C_{3-10} cycloalkyl; a 3-8 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen; phenyl; a 5 or 6 membered heterocyclic aryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur or nitrogen; R_9 represents hydrogen and R_{10} represents hydrogen, hydroxy, halo, C_{1-6} alkoxy or C_{1-6} alkyl.

12. A compound according to claim 1 represented by formula VI

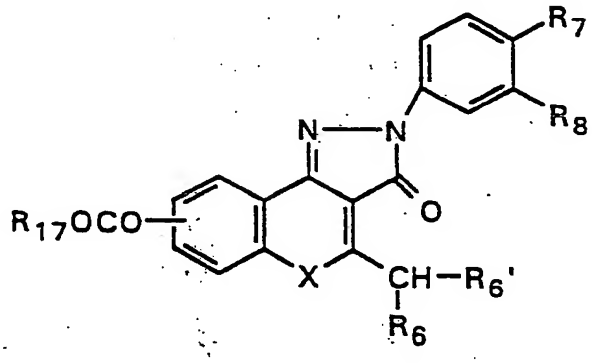


VI

in which R_6' represents hydrogen, R_{14} represents OR_{15}, R_{16} or $NR_{12}R_{13}$ in which R_{12} represents methyl or ethyl, R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen, a 5 or 6 membered heterocyclic aryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur or nitrogen or R_{13}

represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or R_{12} and R_{13} together with nitrogen to which they are attached form a 3-8 membered non-aromatic heterocyclic ring which may contain a further heteroatom selected from oxygen, sulphur or nitrogen which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group; and R_{15} and R_{16}, which may be the same or different, represent optionally substituted groups selected from C_{1-6} alkyl; C_{2-6} alkenyl; C_{3-10} cycloalkyl; a 3-8 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen; phenyl; a 5 or 6 membered heterocyclic aryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur or nitrogen; R_9 represents hydrogen and R_{10} represents hydrogen, hydroxy, halo, C_{1-6} alkoxy or C_{1-6} alkyl.

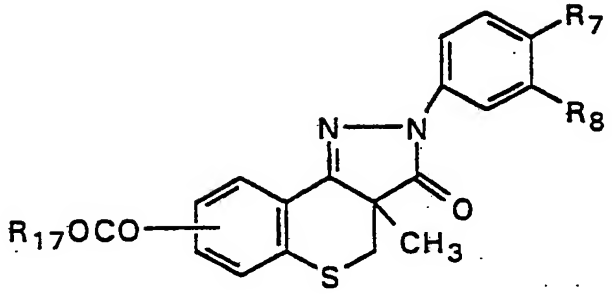
13. A compound according to claim 1 represented by formula VII



VII

in which R_6' represents hydrogen and R_6 represents hydrogen, C_{2-6} alkoxycarbonyl or C_{1-6} alkylthio, R_{17} represents optionally substituted groups selected from C_{1-6} alkyl; C_{2-6} alkenyl; C_{3-11} cycloalkyl; a 3-8 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen; phenyl; a 5 or 6 membered heterocyclic aryl group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen.

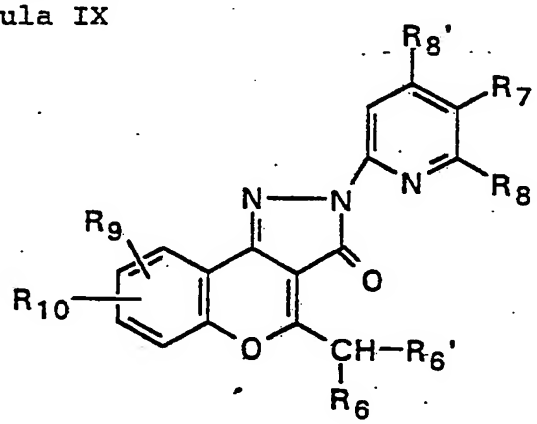
14. A compound according to claim 1 represented by formula VIII



VIII

in which R_{17} represents optionally substituted groups selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, a 3-8 membered non-aromatic heterocyclic group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen; phenyl; a 5 or 6 membered heterocyclic aryl group containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen.

15. A compound according to any one of claims 1-6 represented by formula IX



IX

in which $R_{6'}$ represents hydrogen or methyl; R_6 represents hydrogen, halo, C_{2-6} alkanoyl, C_{2-6} alkoxycarbonyl, $S(O)_nY_1$, carbamoyl, carboxy or R_5 and R_6 together with a carbon atom to which they are attached represent cyclopropyl; R_7 represents hydrogen, halo, trifluoromethyl, methoxy, C_{1-6} alkyl, $S(O)_mY_1$; R_8 represents hydrogen, halo or trifluoromethyl; $R_{8'}$

represents hydrogen, halo or trifluoromethyl; R_9 and R_{10}, which may be the same or different, each represent halo; or R_9 represents hydrogen and R_{10} represents hydrogen, halo, trifluoromethyl, hydroxy, nitro, C_{2-6} alkanoyloxy, C_{1-6} alkyl or C_{1-6} alkoxy.

16. A compound selected from:-

cyclobutylmethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate

2-hydroxyethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate

2-thiomorpholinoethyl 2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazole-4-acetate

2-(4-chlorophenyl)-4-(2-oxo-3-phenoxypropyl)[1]-benzopyrano[4,3-c]pyrazol-3(2H)-one

2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazol-8-yl (3-methylthio)-propionate

2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazol-8-yl dimethylamino acetate

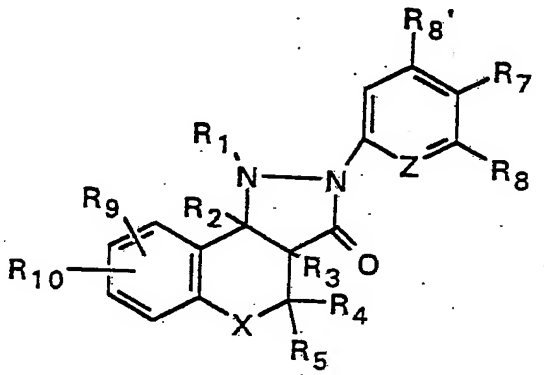
Ethyl 8-acetoxyacetoxy-2-(4-chlorophenyl)-3-oxo-2,3-dihydro[1]benzopyrano[4,3-c]pyrazol-4-acetate

2-(4-chlorophenyl)-4-methyl-3-oxo-2,3-dihydro[1]-benzopyrano[4,3-c]pyrazol-8-yl ethyl malonate

2-(3,4-dichlorophenyl)-3a-methyl-3-oxo-2,3,3a,4-

tetrahydro[1]benzothiopyrano[4,3-c]pyrazol-8-yl methoxy acetate.

17. A pharmaceutical composition comprising a compound of formula I



I

in which X represents oxygen or sulphur;

when X represents oxygen or sulphur R_1 represents hydrogen or together with R_2 represents a bond; R_2 together with either one of R_1 and R_3 represents a bond; R_3 together with either one of R_2 and R_4 represents a bond; R_4 represents hydrogen or together with R_3 represents a bond;

or when X represents sulphur, R_1 and R_2 represent a bond, R_3 represents methyl and R_4 and R_5 represent hydrogen;

Z represents -CH= or -N= when X represents oxygen;

Z represents -CH= when X represents sulphur;

R_5 represents hydrogen when R_3 represents methyl,

or R_5 represents $\overset{R_6}{\underset{|}{CH}} - R_6$,

when R_3 represents a bond together with either one of R_2 and R_4;

R_6 represents hydrogen, halo, $S(O)_nY_1$, carboxy, carbamoyl, carboxylic acyl group, an esterified carboxyl group or $CONR_{12}R_{13}$;

$R_{6'}$ represents hydrogen or methyl;

or R_6 and $R_{6'}$ together with the carbon atom to which they are attached represent cyclopropyl;

R_7 represents hydrogen, halo, trifluoromethyl, C_{1-6} alkyl, methoxy or $S(O)_mY$;

R_8 represents hydrogen, halo or trifluoromethyl;

$R_{8'}$ represents hydrogen, halo or trifluoromethyl;

R_9 and R_{10}, which may be the same or different, represent halo; or R_9 represents hydrogen and R_{10} represents hydrogen, halo, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or a carboxylic acyloxy group;

R_{12} represents methyl, or ethyl or C_{3-8} cycloalkyl and R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocylic group, a 5 or 6 membered heterocyclic aryl group or C_{3-8} cycloalkyl, or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or

R_{12} and R_{13} together with the nitrogen with to which they are attached represent a 3-8 membered non-aromatic heterocylic group which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group;

Y_1 represents C_{1-6} alkyl;
n is 0, 1 or 2 and m is 0 or 1

or a pharmaceutically acceptable salt thereof, provided that:

I) when X is oxygen, Z is -CH= and:

a) R_6 represents C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy; or

b) when R_6 represents hydrogen, halo, $S(O)_nY_1$, carbamoyl, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkanoyl or when R_6 and R_6, together with the carbon atom to which they are attached form cylopropyl then R_{10} represents a carboxylic acyloxy group other than C_{2-6} alkanoyloxy;

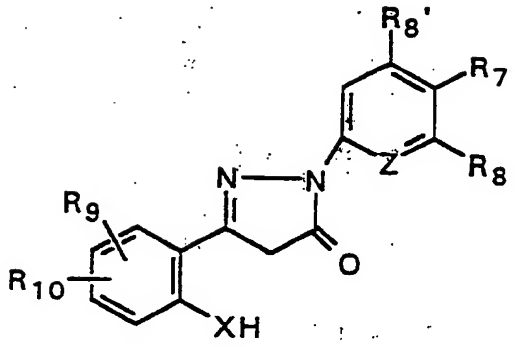
II) When X is sulphur, Z is -CH=, and a) R_3 represents methyl; or b) R_6 represents hydrogen, carboxy, $S(O)_nY_1$, C_{2-6} alkoxycarbonyl, carbamoyl or C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy.

18. A pharmaceutical composition according to claim 17 in unit dosage form.

19. A method of treating diseases with an immunological association in a mammal in need of such treatment comprising the administration of a therapeutically effective amount of a compound of formula I as defined in claim 17.

20. A compound of formula I as defined in claim 17 for use as an immunomodulatory agent.

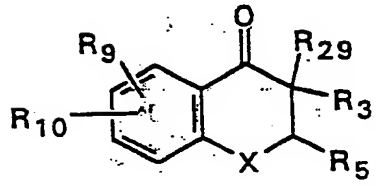
22. A compound of formula X



X

in which R_7, R_8, R_8', R_9 and R_{10} are as defined in claim 1 and Z is nitrogen.

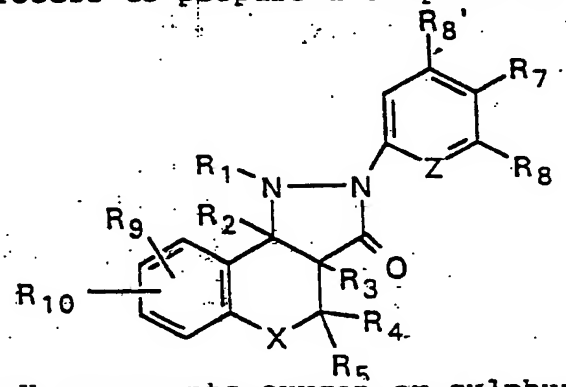
22. A compound of formula XIV



XIV

in which R_3, R_5 and R_9 are as defined in claim 1 and R_{10} represents a carboxylic acyloxy group, R_{29} represents carbamoyl or $COOR_{30}$ and R_{30} represents C_{1-4} alkyl or benzyl.

23. A process to prepare a compound of formula I



I

in which X represents oxygen or sulphur;

R_1 together with R_2 represents a bond; R_3 together with R_4 represents a bond;

Z represents -CH= or -N= when X represents oxygen;

Z represents -CH= when X represents sulphur;

R_5 represents $CH - R_6$, with R_6 below the CH;

R_6 represents hydrogen, halo, $S(O)_nY_1$, carboxy, carbamoyl, a carboxylic acyl group, an esterified carboxyl group or $CONR_{12}R_{13}$;

$R_{6'}$ represents hydrogen or methyl;

or R_6 and $R_{6'}$ together with the carbon atom to which they are attached represent cyclopropyl;

R_7 represents hydrogen, halo, trifluoromethyl, C_{1-6} alkyl, methoxy or $S(O)_mY_1$;

R_8 represents hydrogen, halo or trifluoromethyl;

$R_{8'}$ represents hydrogen, halo or trifluoromethyl;

R_9 and R_{10}, which may be the same or different, represent halo; or R_9 represents hydrogen and R_{10} represents hydrogen, halo, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or a carboxylic acyloxy group;

R_{12} represents methyl, ethyl or C_{3-8} cycloalkyl and R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocylic group, a 5 or 6 membered heterocyclic aryl group or C_{3-8} cycloalkyl or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or

R_{12} and R_{13} together with the nitrogen to which they are attached represent a 3-8 membered non-aromatic heterocylic group which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group;

Y_1 represents C_{1-6} alkyl;

n is 0, 1 or 2 and m is 0 or 1;

or a pharmaceutically acceptable salt thereof;

provided that:

I) when X is oxygen, Z is -CH= and:

a) R_6 represents C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy; or

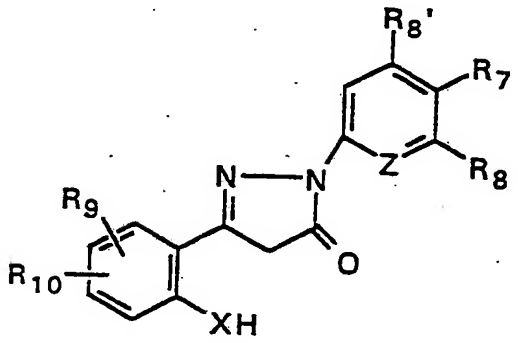
b) when R_6 represents hydrogen, halo, $S(O)_nY_1$, carbamoyl, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkanoyl or when R_6 and $R_{6'}$ together with the carbon atom to which they are attached form cylopropyl then R_{10} represents a carboxylic acyloxy group other than C_{2-6} alkanoyloxy; or

c) when R_1 and R_2 form a bond, R_3 and R_4 form a bond, $R_{6'}$, R_8, $R_{8'}$, R_9 and R_{10} each represent hydrogen, R_7 represents chloro, then R_6 does not represent 4-methoxybenzyloxycarbonyl; or

II) When X is sulphur and R_6 represents hydrogen, carboxy, $S(O)_nY_1$, C_{2-6} alkoxycarbonyl, carbamoyl, or C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy:-

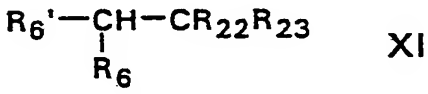
a) comprising oxidising a compound of formula I in which R_1 represents hydrogen, R_2 and R_3 represent a bond and R_4 represents hydrogen and X, Z, R_5, R_7, R_8, $R_{8'}$, R_9 and R_{10} are as herein defined;

b) comprising reacting a compound of formula X



X

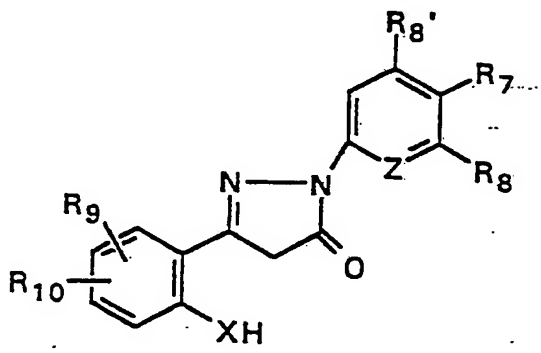
or a tautomer thereof, with a compound of formula XI



XI

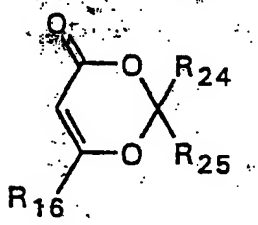
in which R_{22} represents $(OQ)_2$ and R_{23} represents OQ or NQ'_2; or R_{22} represents $(SQ)_2$ and R_{23} represents SQ or NQ'_2; or R_{22} represents =NH and R_{23} represents OQ or SQ; or R_{22} represents =O and R_{23} represents a leaving group and Q and Q' represent a C_{1-4} alkyl group or a benzyl group;

c) in which R_6 is selected from a carboxylic acyl group comprising reacting a compound of formula X



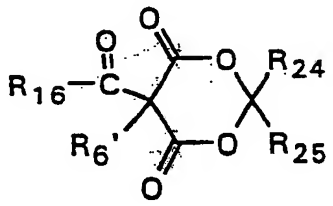
X

with a compound of formula XIIa



XIIa

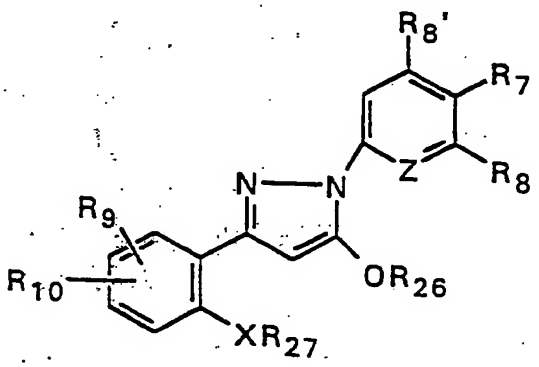
or a tautomer thereof, or a compound of formula XIIb



XIIb

or a tautomer thereof, in which R_{16} represents an optionally substituted group selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, a 3-8 membered non-aromatic heterocyclic group, a carbocyclic aryl group or a 5 or 6 membered heterocyclic aryl group and R_{24} and R_{25} which may be the same or different, represent a C_{1-6} alkyl group or a benzyl group;

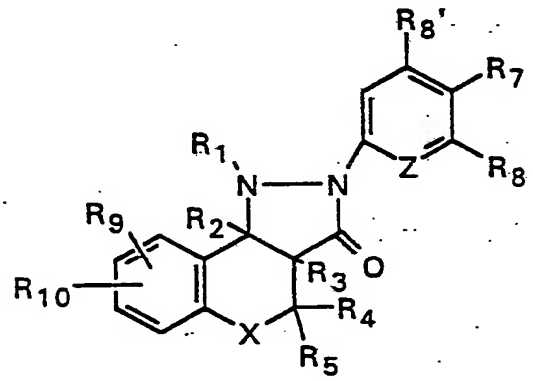
d) comprising reacting a compound of formula XIII



XIII

in which R_{26} represents hydrogen or a tautomer thereof, or in which R_{26} represents a group COR_{28} in which R_{28} represents hydrogen, an optionally substituted C_{1-4} alkyl group or benzyl and R_{27} represents $COCHR_6R_{6'}$, with a base.

24. A process to prepare a compound of formula I



I

in which X represents oxygen or sulphur;

R_1 represents hydrogen; R_2 together with R_3 represents a bond; R_4 represents hydrogen;

Z represents -CH= or -N= when X represents oxygen;

Z represents -CH= when X represents sulphur;

R_5 represents $CH - R_6$, R_6

R_6 represents hydrogen, halo, $S(O)_nY_1$, carboxy, carbamoyl, a carboxylic acyl group, an esterified carboxyl group or $CONR_{12}R_{13}$;

$R_{6'}$ represents hydrogen or methyl;

or R_6 and $R_{6'}$ together with the carbon atom to which they are attached represent cyclopropyl;

R_7 represents hydrogen, halo, trifluoromethyl, C_{1-6} alkyl, methoxy or $S(O)_mY_1$;

R_8 represents hydrogen, halo or trifluoromethyl;

$R_{8'}$ represents hydrogen, halo or trifluoromethyl;

R_9 and R_{10}, which may be the same or different, represent halo; or R_9 represents hydrogen and R_{10} represents hydrogen, halo, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or a carboxylic acyloxy group;

R_{12} represents methyl, ethyl or C_{3-8} cycloalkyl and R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocylic group, a 5 or 6 membered heterocyclic aryl group or C_{3-8} cycloalkyl, or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or

R_{12} and R_{13} together with the nitrogen to which they are attached represent a 3-8 membered non-aromatic heterocylic group which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group;

Y_1 represents C_{1-6} alkyl;

n is 0, 1 or 2 and m is 0 or 1;

or a pharmaceutically acceptable salt thereof;

provided that:

I) when X is oxygen, Z is -CH= and:

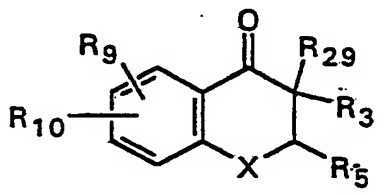
a) R_6 represents C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy; or

b) when R_6 represents hydrogen, halo, $S(O)_nY_1$, carbamoyl, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkanoyl or when R_6 and $R_{6'}$ together with the carbon atom to which they are attached form cylopropyl then R_{10} represents a carboxylic acyloxy group other than C_{2-6} alkanoyloxy; or

II) When X is sulphur and R_6 represents hydrogen, carboxy, $S(O)_nY_1$, C_{2-6} alkoxycarbonyl, carbamoyl, or C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy:-

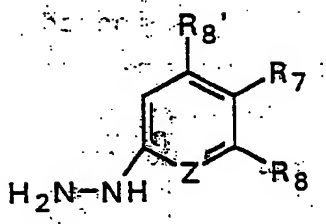
a) comprising reducing a compound of formula I wherein R_1 and R_2 represents a bond; R_3 and R_4 represent a bond; and R_5, R_7, R_8, $R_{8'}$, R_9 and R_{10} are as herein defined; or

b) comprising reacting a compound formula XIV



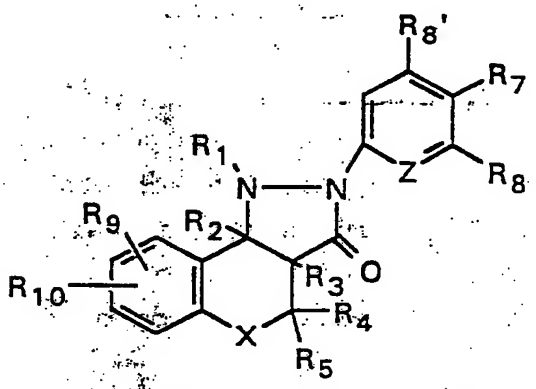
XIV

in which R_3 represents hydrogen, R_5 represents $CHR_6R_{6'}$, R_{29} represents $COOR_{30}$ or carbamoyl and R_{30} represents a C_{1-4} alkyl group or a benzyl group with a compound of formula XV



XV

25. A process to prepare a compound of formula I



I

in which X represents sulphur, R_1 and R_2 represent a bond, R_3 represents methyl and R_4 and R_5 represent hydrogen;

Z represents -CH=;

R_7 represents hydrogen, halo, trifluoromethyl, C_{1-6} alkyl, methoxy or $S(O)_mY_1$;

R_8 represents hydrogen, halo or trifluoromethyl;

$R_{8'}$ represents hydrogen, halo or trifluoromethyl;

R_9 and R_{10}, which may be the same or different, represent halo; or R_9 represents hydrogen and R_{10} represents hydrogen, halo, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or a carboxylic acyloxy group;

R_{12} represents methyl, ethyl or C_{3-8} cycloalkyl and R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocylic group, a 5 or 6 membered heterocyclic aryl group or C_{3-8} cycloalkyl or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or

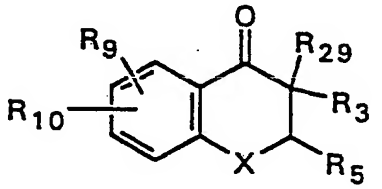
R_{12} and R_{13} together with the nitrogen to which they are attached represent a 3-8 membered non-aromatic heterocylic group which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group;

Y_1 represents C_{1-6} alkyl;

n is 0, 1 or 2 and m is 0 or 1;

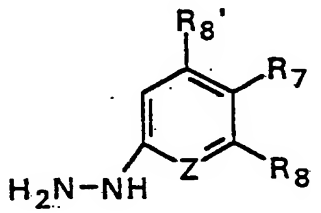
or a pharmaceutically acceptable salt thereof, provided that R_{10} represents a carboxylic group other than acetoxy,

comprising reacting a compound of formula XIV



XIV

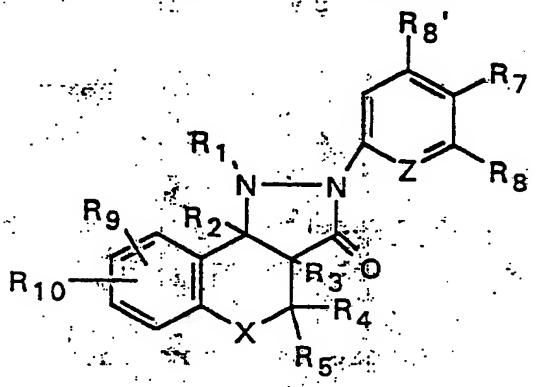
in which R_3 represents methyl, X represents S, R_5 represents hydrogen R_{29} represents $COOR_{30}$ or carbamoyl and R_{30} represents a C_{1-4} alkyl group or a benzyl group with a compound of formula XV



XV

in which Z represents -CH=.

26. A process to prepare a compound of formula I



I

in which X represents oxygen or sulphur;

when X represents oxygen or sulphur R_1 represents hydrogen or together with R_2 represents a bond; R_2 together with either one of R_1 and R_3 represents a bond; R_3 together with either one of R_2 and R_4 represents a bond; R_4 represents hydrogen or together with R_3 represents a bond;

or when X represents sulphur, R_1 and R_2 represent a bond, R_3 represents methyl and R_4 and R_5 represent hydrogen;

Z represents -CH= or -N= when X represents oxygen;

Z represents -CH= when X represents sulphur;

R_5 represents hydrogen when R_3 represents methyl,

or R_5 represents $CH - R_6$, with R_6 below the CH,

when R_3 represents a bond together with either one of R_2 and R_4,

R_6 represents hydrogen, halo, $S(O)_nY_1$, carboxy, carbamoyl, a carboxylic acyl group, an esterified carboxyl group or $CONR_{12}R_{13}$;

$R_{6'}$ represents hydrogen or methyl;

or R_6 and $R_{6'}$ together with the carbon atom to which they are attached represent cyclopropyl;

R_7 represents hydrogen, halo, trifluoromethyl, C_{1-6} alkyl, methoxy or $S(O)_mY_1$;

R_8 represents hydrogen, halo or trifluoromethyl;

$R_{8'}$ represents hydrogen, halo or trifluoromethyl;

R_9 and R_{10}, which may be the same or different, represent halo; or R_9 represents hydrogen and R_{10} represents hydrogen, halo, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or a carboxylic acyloxy group;

R_{12} represents methyl, ethyl or C_{3-8} cycloalkyl and R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocylic group, a 5 or 6 membered heterocyclic aryl group or C_{3-8} cycloalkyl; or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or

R_{12} and R_{13} together with the nitrogen to which they are attached represent a 3-8 membered non-aromatic heterocylic group which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group;

Y_1 represents C_{1-6} alkyl;
n is 0, 1 or 2 and m is 0 or 1;

or a pharmaceutically acceptable salt thereof; provided that:

I) when X is oxygen, Z is -CH= and:

a) R_6 represents C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy; or

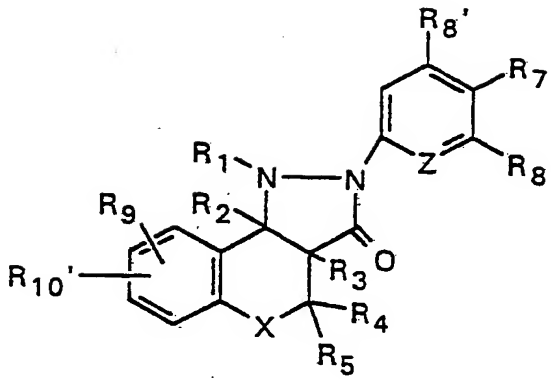
b) when R_6 represents hydrogen, halo, $S(O)_nY_1$, carbamoyl, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkanoyl or when R_6 and R_6' together with the carbon atom to which they are attached form cylopropyl then R_{10} represents a carboxylic acyloxy group other than C_{2-6} alkanoyloxy; or

c) when R_1 and R_2 form a bond, R_3 and R_4 form a bond, R_6'', R_8, R_8', R_9 and R_{10} each represent hydrogen, R_7 represents chloro, then R_6 does not represent 4-methoxybenzyloxycarbonyl; or

II) When X is sulphur and a) R_3 represents methyl; or

b) R_6 represents hydrogen, carboxy, $S(O)_nY_1$, C_{2-6} alkoxycarbonyl, carbamoyl, or C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy:-

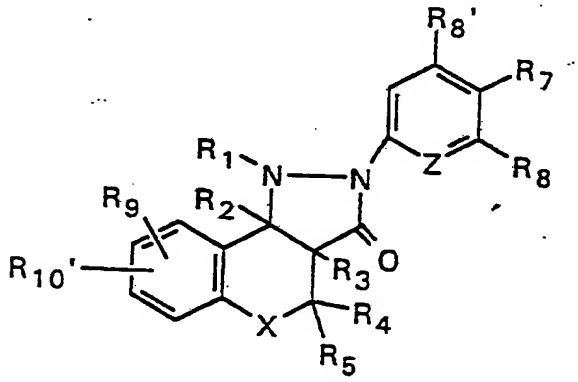
a) in which R_5 represents $-CHR_6R_6'$ and R_6 is selected from $CONR_{12}R_{13}$ or an esterified carboxyl group, comprising reacting a compound of formula I'



I'

in which R_{10}' represents R_{10}, R_5 represents $-CHR_aR_6$,, R_a represents COA and A represents a leaving group, with an amine of formula $NHR_{12}R_{13}$ or an alcohol of formula $R_{15}OH$ in which R_{15} represents an optionally substituted group selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, a 3-8 membered non-aromatic heterocyclic group, a carbocyclic aryl group or a 5 or 6 membered heterocyclic aryl group respectively;

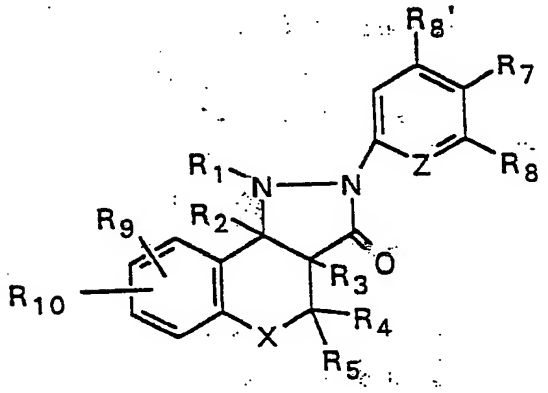
b) in which R_{10} is selected from a carboxylic acyloxy group comprising reacting a compound of formula I'



I'

in which R_5 represents $-CHR_aR_6$', R_a represents R_6 and R_{10}' represents hydroxy with an acylating agent.

27. A compound of formula I



I

in which X represents oxygen or sulphur;

when X represents oxygen or sulphur R_1 represents hydrogen or together with R_2 represents a bond; R_2 together with either one of R_1 and R_3 represents a bond; R_3 together with either one of R_2 and R_4 represents a bond; R_4 represents hydrogen or together with R_3 represents a bond;

or when X represents sulphur, R_1 and R_2 represent a bond, R_3 represents methyl and R_4 and R_5 represent hydrogen;

Z represents -CH=;

R_5 represents hydrogen when R_3 represents methyl,

or R_5 represents $CH - R_6$, with R_6 below the CH,

when R_3 represents a bond together with either one of R_2 and R_4;

R_6 represents hydrogen, halo, $S(O)_nY_1$, carboxy, carbamoyl, a carboxylic acyl group, an esterified carboxyl group or $CONR_{12}R_{13}$;

$R_{6'}$ represents hydrogen or methyl;

or R_6 and $R_{6'}$ together with the carbon atom to which they are attached represent cyclopropyl;

R_7 represents hydrogen, halo, trifluoromethyl, C_{1-6} alkyl, methoxy or $S(O)_mY_1$;

R_8 represents hydrogen, halo or trifluoromethyl;

$R_{8'}$ represents hydrogen, halo or trifluoromethyl;

R_9 and R_{10}, which may be the same or different, represent halo; or R_9 represents hydrogen and R_{10} represents hydrogen, halo, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or a carboxylic acyloxy group;

R_{12} represents methyl or ethyl and R_{13} represents C_{1-6} alkyl optionally substituted by cyano, phenyl, a 3-8 membered non-aromatic heterocylic group, a 5 or 6 membered heterocyclic aryl group; or R_{13} represents phenyl optionally substituted by C_{2-6} alkoxycarbonyl or halo; or

R_{12} and R_{13} together with the nitrogen to which they are attached represent a 3-8 membered non-aromatic

heterocylic group which may be substituted by a C_{2-6} acyloxy(C_{1-6})alkyl group;

Y_1 represents C_{1-6} alkyl;
n is 0, 1 or 2 and m is 0 or 1;
or a pharmaceutically acceptable salt thereof;
provided that:

I) when X is oxygen and:

a) R_6 represents C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy; or

b) when R_6 represents hydrogen, halo, $S(O)_nY_1$, carbamoyl, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkanoyl or when R_6 and R_6' together with the carbon atom to which they are attached form cyclopropyl then R_{10} represents a carboxylic acyloxy group other than C_{2-6} alkanoyloxy; or

c) when R_1 and R_2 form a bond, R_3 and R_4 form a bond, R_6'', R_8, R_8'', R_9 and R_{10} each represent hydrogen, R_7 represents chloro, then R_6 does not represent 4-methoxybenzyloxycarbonyl; or

II) When X is sulphur and a) R_3 represents methyl; or b) R_6 represents hydrogen, carboxy, $S(O)_nY_1$, C_{2-6} alkoxycarbonyl, carbamoyl, or C_{1-6} dialkylcarbamoyl, then R_{10} represents a carboxylic acyloxy group other than acetoxy.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/00154

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 D 491/052,495/04,311/22,335/06,405/04,409/04; //(C 07 D 491/052,311:00,231:00); (C 07 D 495/04, 335:00, 231:00)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D 491/00,C 07 D 495/00,C 07 D 311/00, C 07 D 335/00,C 07 D 405/00,C 07 D 409/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4 268 516 (LOMBARDINO et al.) 19 May 1981 (19.05.81), see claims 1,11,17. --	1,12, 17,18, 23-27
A	Chemical Abstracts, Volume 111, no. 9, issued 1989, August 28 (28.08.89) (Columbus, Ohio, USA) Colotta, V. et al. "Tricyclic heteroarometic systems: synthesis, (3H) flunitrazepam brain membrane binding inhibition, and structure-activity relationships of 2,3-dihydro-2-aryl-4-R- (1)benzopyrano(4,3-c) pyrazol-3-ones", see page 16, column 2, abstract no. 70 311m, J. Pharm. Sei. 1989, 78(3), 239-42 (Eng) --	1,12, 17,18, 23-27

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10 April 1991	17 MAY 1991
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	MISS D. S. KOWALCZYK

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Chemical Abstracts, Volume 106, no. 15, issued 1987, April 13 (13.04.87) (Columbus, Ohio, USA) Ghosh, C.K. et al. "Benzopyrans. Part XX. 4-Oxo-4H-(1)benzopyran-3-carbonitrile/carboxylic acid: change of their reaction courses by a methyl substituent at the 2-position", see page 619, column 2, the abstract no. 119 619f, Indian J. Chem., Sect. B 1985, 24 B(12), 1288-90 (Eng)	1,12, 17,18, 21-27

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 19, because they relate to subject matter not required to be searched by this Authority, namely:

see PCT Rule 39.1(iv) (Method for treatment of the human or animal body by therapy)

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANHANG
zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX
to the International Search Report to the International Patent Application No.

ANNEXE
au rapport de recherche international relatif á la demande de brevet international n°

SA44057

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les reseignements fournis sont donnés á titre indicatif et n'engagent pas la responsibilité de l'Office.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US-A - 4268516	19-05-81	Keine - None - Rien	